Original Article

Effects of wheat flour fortified with different iron fortificants on iron status and anemia prevalence in iron deficient anemic students in Northern China

Jing Sun BD[1], Jian Huang BD[1], Wenxian Li BD[1], Lijuan Wang MD[1], Anxu Wang MD[2], Junsheng Huo PhD[1], Junshi Chen MD[1] and Chunming Chen BD[1]

[1]*Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, Beijing 100050, China*
[2]*Wancheng Center of Disease Control and Prevention*

Objectives: To compare the effects of wheat flours fortified with NaFeEDTA, $FeSO_4$ and elemental iron (electrolytic iron), in improving iron status in anemic students. Methods: Four hundreds anemic students (11 to 18 years old) were divided into four groups and given wheat flour fortified with different iron fortificants at different concentrations: control group (no added iron); NaFeEDTA group (20 mg Fe/kg); $FeSO_4$ group (30 mg Fe/kg); and elemental iron group (60 mg Fe/kg). The trial lasted for 6 months and the following parameters were examined every 2 months: whole blood hemoglobin, free erythrocyte protoporphyrin, serum ferritin, serum iron, total iron binding capacity and transferrin receptor. Results: The flour consumption in the 4 groups was 300-400 g/person/day, accounted for 70% of total cereal consumption in the diets. There were no significant differences in flour consumption among the 4 groups. Blood hemoglobin level increased in all the 3 intervened groups, but the increment in the NaFeEDTA group was significantly higher and earlier than the other 2 groups; and only 1% of the subjected remained anemic at the end of the trial in the NaFeEDTA group, while 40% and 60% of the subjects in the $FeSO_4$ and electrolytic iron group remained anemic, respectively. The order of improvements in free erythrocyte protoporphyrin, serum ferritin and transferring receptor levels were: NaFeEDTA > $FeSO_4$ > electrolytic iron. No significant changes were found in the control group on all the tested parameters during the trial. Conclusions: The results indicated that even when NaFeEDTA was added at a lower level, it has better effects than $FeSO_4$ and elemental iron in controlling iron deficiency anemia and improving iron status in anemic children; while elemental iron was the least effective.

Key Words: NaFeEDTA, $FeSO_4$, elementary iron, iron deficiency anemia, wheat flour, food fortification

Introduction

Iron deficiency (ID) and iron deficiency anemia (IDA) are major nutrition problems around the whole world with impact on new born infant mortality, physical and mental growth retardation of children, reduction of productivity of adults and susceptibility to infectious diseases.[1-3] Flour fortification with iron and other nutrients has been practiced in many countries. However, flour fortification with iron remains an important issue in regard to absorption and efficacy. Elementary iron and $FeSO_4$ are the common iron sources for flour fortification and in recent years NaFeEDTA has been preferred to fortify high extraction flour.[4-7] The concerns about low bioavailability of elementary iron,[8] high cost of NaFeEDTA [9, 10] and possible impact of $FeSO_4$ [11, 12, 13] on quality and storage on food vehicles by oxidation should be based on more scientific evidence. This study is designed to differentiate the efficacy by electrolytic iron, $FeSO_4$ and NaFeEDTA fortified flour on ID and IDA in anemic students. Such information is required before further promotion of flour fortification

Materials and Methods

Wheat flour

Grade I wheat flour, extraction rate 70%, was used as the basal flour. Three different kinds of flour were produced from basal flour, which were electrolytic iron fortified flour, $FeSO_4$ fortified flour and NaFeEDTA fortified flour. Three fortified flour and basal flour supplied to four groups of subjects freely during the observation period. The levels of iron fortified as recommended commonly were electrolytic iron 60 mg Fe/kg, $FeSO_4$ 30 mg Fe/kg and NaFeEDTA 20 mg Fe/kg respectively. Electrolytic iron and FeSO4 were provided by SUSTAIN, and NaFeEDTA was provided by Beijing Vita Sci-Tech Co., Ltd. (in compliance with the JECFA specifications[14]). The contents of iron in electrolytic iron, $FeSO_4$ and NaFeEDTA are 98%, 32% and13% respectively.

Corresponding Author: Dr Lijuan Wang, Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, 29 Nan Wei Road, Beijing 100050, China.
Tel: 8610-8313-2383; Fax: 8610-8313-2317
Email: wljcdc@sohu.com
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Subjects and treatments

Four hundred and nine school students, aged 11 to 18 years old, were diagnosed as IDA from 4,500 students in 4 schools in Nanyang city, Henan province and were divided into four groups on school basis and supplied with wheat flour fortified with different iron fortificants. The four groups were control group, 109 students (47 males, 62 females); electrolytic iron group, 96 students (42 males, 54 females); $FeSO_4$ group, 107 students (44 males, 63 females); NaFeEDTA group, 106 students (42 males, 64 females). The World Health Organization diagnostic criteria for IDA were used for the diagnosis of anemia.[15] The four groups were located in four nearby schools in the same area with similar economic level, lifestyle and dietary pattern. The subjects took meals together in the boarding schools, except during one-month holidays. The fortified and basal flour were also freely supplied to the families of subjects so that the subjects had the same flour consumed in family in holidays. The intervention lasted 6 months.

The study protocol was reviewed and approved by the Ethical Committee of the Institute of Nutrition and Food Hygiene, Chinese Center for Disease Control and Prevention. Volunteer forms were obtained from each subject and their guardian.

Survey and measurement

Food consumption data was collected at the beginning and end of the study, using a validated food frequency questionnaire with reference to the food records provided by the cafeteria of each school. The dietary iron intake was calculated from the Chinese Food Composition Tables.[16] Body weight and height were measured at the beginning and end of the study. The following blood parameters were measured every 2 months started from the baseline survey: whole blood hemoglobin (Hb), serum iron (SI), ferritin (SF), transferrin receptor (TfR) and total iron binding capability (TIBC), and blood free erythrocyte protoporphyrin (FEP).

Hb was measured by Hemocue B-Hemoglobin system made by Hemocue AB Corporation, Sweden.

Five ml of intravenous blood was collected from each subject and from which 20 µl blood was dropped onto a piece of filter paper for the FEP measurement. The remaining intravenous blood was centrifuged at 3,000 rpm for 20 min. And the separated serum was stored at -20 °C for measurements of SI, TIBC, SF, TfR.

For the measurement of FEP, 20 µL intravenous blood was dropped onto a piece of filter paper and detected by fluorometry with excitation wavelength at 403 nm and emission wavelength at 605 nm.[17]

Test kits from the RANDOX Company, England, were used to measure: SI (colorimetry at 546 nm), SF (turbidity at 700 nm) and TIBC (turbidity at 600 nm) by auto-biochemical analyzer (Hitachi 7060), using the standards and calibrating reagents provided by RANDOX Company. TfR was measured by the ELISA method at 450 nm, corrected at 540 nm, using a Bio-Rad microplate manager spectrophotometer, R&D System, Inc. America.

Statistical analysis of data

Data analysis was conducted by analysis of variance (ANOVA) with the SPSS software. The statistical analysis for the TfR was carried out on logarithm transformed values.

Results

General status of the subjects

All the tested flours were well accepted by the subjects and no side effects were observed through out the 6 months study. Body weight and height of the subjects increased slightly during the trial, but there were no significant differences among the 4 groups (data not shown).

Dietary patterns and food consumption

The diet that the subjects consumed is a typical plant-food-based diet of north central China. There was no difference in the food consumption among the four groups during the trial (Table 1). Average flour consumption of subjects was 316-368 g/day accounting for 70% of the total cereal grain consumption. Average iron intake from the basal diet (excluded added iron) was 20-23 mg/person/day. Average iron intake from the diet including added iron at 6-month was shown in Table 1.

Hemoglobin and anemic rate

The changes of Hb levels in the four groups during the trial were shown in Table 2. Before intervention, the Hb levels were not statistically different among the four groups, and Hb level of the control group remained unchanged in 6 months. Hb level of the NaFeEDTA group was increased significantly from month 2 till month 6. Hb level of the $FeSO_4$ group became significantly higher at month 4 and month 6 than that of baseline and control group. The Hb level of the electrolytic iron group did not increase significantly until 6 months after the beginning of the trial, and the increment was significantly less than the other 2 iron fortified groups. By the end of the month 6, the rate of IDA in the control group remained unchanged (93.3%), while only 1 student (1%) remained IDA in the NaFeEDTA group, and 40% and 60% students remained IDA in the $FeSO_4$ and electrolytic iron groups respectively.

Serum iron

SI levels of control and electrolytic iron groups did not change significantly during the intervention period. However, the SI level of the NaFeEDTA and FeSO4 group increased significantly after month 4, and the increment was 3.5 and 3.7 µmol/L respectively at month 6 (Table 2).

Serum ferritin

SF level of the control and electrolytic iron groups did not change significantly during trial period. However, SF level of the NaFeEDTA group increased significantly after month 4, while SF level of the FeSO4 group did not increase significantly until the end of the trial. The incre ments of SF levels in NaFeEDTA and FeSO4 groups were 14.0 and 9.5 µg/L respectively at month 6 compared with their baseline. The SF levels of the NaFeEDTA and

Table l. Comparison of food consumption through out the study and among different groups (g/person/day)

	Control group		NaFeEDTA group		$FeSO_4$ group		Electrolytic iron group	
	0 month	6 months	0 month	6 months	0 month	6 months	0 month	6 months
Rice	42.0±53.5	46.3±38.2	36.83±53.0	38.0±51.3	44.7±64.3	42.4±45.6	42.8±77.2	48.1±52.7
Wheat flour	317.8±204.5	315.8±106.7	334.6±149.5	328.4±109.1	367.7±148.3	366.9±94.1	359.1±186.5	367.4±104.1
Other grains	76.6±149.9	79.8±86.3	79.9±98.0	66.7±60.8	78.7±108.9	73.0±44.4	71.7±112.4	73.5±71.7
Tubers	77.7±93.9	70.8±41.3	79.9±86.4	68.1±70.2	88.1±108.5	70.8±26.9	58.5±74.6	69.1±51.2
Meat and poultry	51.2±69.4	52.7±79.5	44.9±51.7	54.0±40.8	45.0±31.0	53.4±18.9	42.3±91.7	57.8±36.2
Eggs	40.9±66.2	31.1±30.1	33.3±35.4	28.8±40.5	30.2±41.2	32.2±44.7	33.8±24.0	27.8±29.5
Milk and product	52.8±93.8	45.2±54.8	49.1±102.5	36.8±28.4	32.7±61.3	37.4±18.5	43.2±98.7	30.6±71.2
Fishes	8.1±12.1	7.3±14.0	6.0±10.4	4.0±6.6	5.0±15.8	6.2±3.6	6.6±10.9	5.3±15.9
Vegetables	229.2±171.1	271.4±175.9	269.6±162.4	248.9±168.2	243.9±166.3	211.6±81.0	216.3±189.8	219.7±144.8
Fruits	63.3±126.1	65.3±66.6	65.4±89.7	87.2±45.4	69.4±69.7	62.4±26.4	70.0±90.0	54.5±42.5
Beans	75.0±87.3	74.3±95.8	68.7±93.0	51.8±43.5	79.6±63.1	65.7±28.5	73.1±120.3	88.3±112.5
Fe (mg)	22.6±14.7	23.0±7.2	20.8±9.4	26.7±5.2	22.7±11.3	31.5±4.3	22.7±10.2	42.9±6.9

Table 2. Changes of blood parameters during the 6 months intervention trial

Groups	Month	Hemoglobin (g/L)	IDA (%)	Reduction %IDA	FEP (×10 μg/L)	Serum iron (μmol/L)	Serum Ferritin (μg/L)	TIBC (μmol/L)	STfR* (nmol/L)
Control	0	114.5±5.3	100		59.0±11.7	11.4±5.2	48.9±19.4	77.6±23.3	36.4±1.2
	2	114.4±8.4	93.6	6.3	59.7±11.1	10.7±5.8	45.6±25.1	76.0±18.9	37.3±1.3
	4	114.8±7.2	95.6	4.3	55.9±12.2	11.9±5.0	47.8±21.4	74.1±15.1	34.3±1.2
	6	114.9±8.0	93.3	6.7	58.0±9.3	11.6±4.7	46.8±23.8	75.0±13.8	35.2±1.3
NaFeEDTA	0	114.9±5.0	100		60.5±10.2	11.3±4.9	46.0±20.5	82.6±34.0	35.7±1.2
	2	118.3±9.3[a]	57.4	42.5	55.3±10.2[aa,bb]	12.4±4.8	47.5±19.6	71.2±21.6[aa]	33.2±1.3[abb]
	4	122.9±9.7[aa,bb]	40	60	42.2±11.1[aa,bb]	14.7±6.5[aa]	55.3±21.3[aa,b]	67.9±15.2[aa,bb]	29.3±1.2[aabb]
	6	132.4±10.2[aa,bb]	1	99	38.1±8.4[aa,bb]	14.8±4.8[aa]	60.0±24.5[aa,bb]	65.4±9.0[aa,bb]	23.0±1.2[aabb]
$FeSO_4$	0	114.5±6.5	100		60.6±9.6	11.2±5.1	49.0±19.8	79.9±21.0	34.6±1.3
	2	117.0±14.4	70.2	29.8	58.4±9.6	10.4±5.8	47.2±30.0	75.7±16.1	33.0±1.3[bb]
	4	118.7±13.5[a,b]	61.9	38.1	46.1±10.1[aa,bb]	13.6±5.3[aa,b]	50.8±19.4	70.4±10.0[aa]	30.0±1.2[aabb]
	6	123.8±13.1[aa,bb]	40	60	42.0±10.5[aa,bb]	14.9±4.7[aa,bb]	58.5±20.9[aa,bb]	67.3±14.1[aa,bb]	26.9±1.2[aabb]
Electrolytic iron	0	114.1±4.7	100		59.8±10.7	11.0±5.3	46.4±17.9	77.2±22.4	36.2±1.2
	2	117.3±8.4	80	20	61.3±11.7	10.2±5.3	43.3±18.9	74.0±14.6	34.4±1.3[b]
	4	117.6±12.4	67.1	32.8	57.8±11.7	11.4±5.8	44.4±20.1	73.1±14.3	33.3±1.2[a]
	6	118.0±10.9[a]	60	40	55.4±8.8[a]	12.0±5.3	48.3±20.4	72.0±17.6	32.6±1.2[aab]

[*] Calculations after logarithmic transformation; [a] $p<0.05$ compared with baseline (0 month); [aa] $p<0.01$ compared with baseline (0 month); [b] $p<0.05$ compared with control group; [bb] $p<0.01$ compared with control group

$FeSO_4$ groups were significantly higher than the control group (p<0.01) after 4 months and 6 months, respectively (Table 2).

Free erythrocyte protoporphyrin

FEP levels of the NaFeEDTA and $FeSO_4$ group decreased and became significantly lower than that of control group at month 4 and 6 (Table 2), while FEP levels of the control and electrolytic iron groups remained unchanged in study period.

Total iron binding capacity

There were no significant changes in TIBC in the control group and electrolytic iron group in the trial. TIBC levels of the NaFeEDTA and $FeSO_4$ group decreased and became significant lower than that of control group and baseline. (Table 2)

Serum transferrin receptor

After log transformation, the data show that after 6 months of intervention, the TfR levels of the control group did not change in the trial. However, the TfR levels of the NaFeEDTA, $FeSO_4$ and electrolytic iron groups decreased significantly at month 4 and 6. The decrements of TfR levels were 12.7, 7.7 and 3.6 nmol/L respectively at month 6 for the NaFeEDTA, $FeSO_4$ and electrolytic iron groups (Table 2).

Discussion

The diets of the subjects were unchanged during the experimental period. The dietary iron intake per subject per day was 20-23 mg which reached the adequate intakes (AI) of the Chinese Nutrition Society for the same age group, i.e. 20-25 mg.[18] The contradiction of the high intake of iron and high IDA prevalence in Chinese population was well documented and it was agreed that the main reason is the low absorption rate of the non-heme iron in plant-food based diet.[18, 19]

The results of this study demonstrated that the Hb level, prevalence of IDA and iron status of the control group was not significantly changed within the 6 months trial. On the other hand, three fortified flours showed positive effects on controlling IDA and improving iron status. The result of this study clearly showed the different impacts of three different iron sources fortified flour.

The fortification of wheat flour with B vitamins and iron could be dated back to more than 70 years before [20]. Elemental iron including reduced iron and electrolytic iron, and $FeSO_4$ are the most widely used iron fortificants in wheat flour fortification,[12, 21, 22, 23] because both are inexpensive and available for a long time. There were a number of reports on absorption or bioavailability of iron in wheat flour [24-30] and those studies revealed that the iron fortificants, such as elemental iron, ferrous sulfate, NaFeEDTA and ferrous fumarate were closely related to the absorption or bioavailability of iron.

In terms of the efficacy and effectiveness of flour fortified with iron in controlling ID and IDA, most studies focused on the intervention effects by consumption of flour fortified with elemental iron, ferrous sulfate and ferrous fumarate. Elwood et al. [31] found that the reduced iron-fortified bread resulted in a small but statistically significant increase in Hb after 9 months of intervention. In another study, Elwood [32] carried out a therapeutic trial in which a group of anemic patients were fed with reduced iron-fortified bread, but no beneficial effect was observed on Hb levels within 3 to 6 months. Researchers believed that the absorption of elemental iron was rather poorer than that of other iron fortificants, furthermore, electrolytic iron was considered a better iron source than reduced iron. [22] The result from this observation showed that electrolytic iron had lower efficacy on ID and IDA than that of $FeSO_4$ and NaFeEDTA.

In the middle of the last century in the South America, the application of ferrous sulfate (30 mg/kg) fortification of flour has successfully reduced the rate of IDA to less than 1% in Chile.[33] Though ferrous sulfate has been used in many iron fortified foods, ferrous sulfate was considered instable in food, effect on organoleptic quality, readily inhibited by iron absorption inhibitors and oxidative on stability of food. Data from this study suggested that $FeSO_4$ had acceptable efficacy on the control of ID and IDA, however recommendation of $FeSO_4$ used in wheat flour might be considered more on the quality aspects by the accumulation of more scientific evidence especially in corn flour and other food categories.

NaFeEDTA, as a new iron fortificant, was overviewed a number of advantages, e.g. high absorption in plant food based diet, less affected by iron absorption inhibitors such as phytic acid and polyphenol, and good stability in food vehicles. However, the relatively high cost of NaFeEDTA limited its use in flour fortification. In recent years, application of NaFeEDTA in varieties of food category such as soy sauce,[9] fish sauce,[10] corn flour, high extraction wheat flour and other fortified food products could possibly reduce its price. In this study, the cost of NaFeEDTA for 1 kg of flour at the level of 20 mg/kg was 0.00092 USD, the cost of $FeSO_4$ for 1 Kg of flour at the level of 30 mg/kg is 0.000225 USD, and the cost of electrolytic iron for 1 Kg of flour at the level of 60 mg/kg is 0.000247 USD. Although the ratio of cost between NaFeEDTA and $FeSO_4$ is 4.1:1, the actual price difference of 1 ton flour fortified with NaFeEDTA and $FeSO_4$ was 0.7 USD, which was believed a negligible differentiation to mills and consumers.

Although a number of indicators of ID and IDA were measured in this study, the critical indicators for the assessment of ID and IDA are blood hemoglobin (Hb), serum ferritin (SF), free erythrocyte protoporphyrin (FEP) and serum transferrin receptor (TfR). Among them, Hb is the only indicator for the assessment of IDA and the other 3 indicators are useful in the assessment of iron status. The result of this study suggested that that NaFeEDTA has the best efficacy in rectifying IDA and improving iron status, and the effects were seen as early as 2 months after the beginning of the trial. $FeSO_4$ was also effective, but not as good as NaFeEDTA. The better efficacy result of NaFeEDTA might related with Chinese diet background which is a typical plant-food-based diet with the high consumption of cereals, fruits and vegetables. The inhibitory factors were derived from the other components of the meals such as phytate and polyphenol. Experts assume the contents of those inhibitors are high enough to influence on the availability of iron from food source.[34, 35, 36] The result of the study suggested that NaFeEDTA was less affected by phytate and polyphenol, which has been discussed by many experts.[37] It is necessary to accumulate more data from efficacy study and technical research on flour fortification so as to have sufficient information for the instructions on flour fortification.

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[1]*Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, Beijing 100050, China*
[2]*Wancheng Center of Disease Control and Prevention*

不同铁剂强化面粉在中国北方改善贫血学生铁缺乏和缺铁性贫血效果

铁缺乏和缺铁性贫血是全球关注的营养问题之一，它具有很多反面效果：致使婴儿死亡率增加，儿童身体和智力发展迟缓，成人生产力下降和易感染等。目前普遍认为食物强化是控制铁缺乏和缺铁性贫血的最为经济、有效、可行的营养干预方式，在许多国家已经开始实行面粉强化。一些专家认为元素铁的吸收率和生物利用率都很低，但是元素铁还是因为其低廉的价格而在面粉强化中广泛使用，此外，硫酸亚铁也被普遍应用。最近 NaFeEDTA 已经被使用在一些食物强化项目中，包括中国的酱油强化和越南的鱼酱强化。在这两个项目中，改善贫血和铁缺乏的生物利用率和效果都是很振奋人心的。本试验的目的为比较以 NaFeEDTA、硫酸亚铁和元素铁（电解质铁）强化面粉改善铁缺乏和缺铁性贫血的效果，为面粉强化选择最合适的铁剂。本试验从河南省南洋市 4 所学校的 4,500 名学生中筛选出 409 名贫血学生（11 到 18 岁），并将这些学生分为 4 组：食用不同剂量的不同铁剂的强化面粉，对照组（不额外加铁）；NaFeEDTA 组 (20 mg Fe/kg)；硫酸亚铁组(30 mg Fe/kg)和元素铁组 (60 mg Fe/kg)，四组学生来源于同一地区相近的 4 所学校，具有相同的经济条件，生活方式和膳食水平。试验持续 6 个月，所研究指标每两个月检测一次，指标包括：血红蛋白，原卟啉，血清铁，铁蛋白，总铁结合力和转铁蛋白受体。试验结果显示：在四组试验人群中，面粉摄入量是 300-400 g/人/天，占总膳食谷物摄入量的 70%，四组试验人群面粉摄入量没有显著性差别。干预 6 个月后，对照组的血红蛋白没有发生显著性变化。而 NaFeEDTA 组在干预 2 个月后血红蛋白开始增长且在干预期间持续增长。$FeSO_4$ 在干预 4 个月后开始增长，且在整个干预阶段持续增长。在干预 6 个月实验结束后，FeSO4 组的血红蛋白水平明显低于 NaFeEDTA 组。元素铁组的血红蛋白在干预 6 个月后有所增长，增长幅度明显低于 FeSO4 和 NaFeEDTA 组。在实验末期，NaFeEDTA 组仅有 1%的学生贫血，而硫酸亚铁组和元素铁组分别有 40%和 60%的实验对象仍然贫血。原卟啉，血清铁，铁蛋白，总铁结合力，转铁蛋白受体水平改善幅度分别是：NaFeEDTA 组>硫酸亚铁组>电解质铁组。对照组所有的参数在试验期间均没有发生显著性的变化。实验结果说明 NaFeEDTA 在添加量很低的水平下比硫酸亚铁和元素铁在改善贫血和铁缺乏上有更好的效果，而元素铁的效果是最差的。

關鍵字：NaFeEDTA, $FeSO_4$,元素铁，铁缺乏贫血，面粉，食物强化