Original Article

Daily and Weekly Iron Supplementations to Improve Iron Status in Infants: A Randomized Controlled Trial

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Background: Iron deficiency anemia screening and iron supplementation in infants aged 6 to12 months are recommended in the Guideline in Child Health Supervision.

Objective: To evaluate the effectiveness of weekly iron supplementation compared with daily supplementation in improving the iron status in infants.

Materials and Methods: A single-blind randomized controlled trial was conducted in infants aged 6 months visiting the Well Child Clinic between May 2019 and November 2020 at Burapha University Hospital, Chonburi, Thailand. The intervention consisted of either daily or weekly iron supplementation combined with iron-rich complementary food promotion for six months. The outcomes were the differences of serum ferritin and hematological variables before and after being iron supplemented.

Results: Sixty-nine of the six-month-old healthy infants were randomized to receive either 10 mg Fe/day as the daily group or 30 mg Fe/week as the weekly group. Forty-five infants with 24 in the daily group and 21 in the weekly group completed the intervention. After the six-month period of iron supplementation, the average differences of serum ferritin in the daily and the weekly group were 10.85 (–13.19, 34.49) and –9.31 (–23.86, –2.30) ng/mL, respectively (p=0.012). The average differences of hemoglobin in the daily and the weekly group were 0.58±0.82 and 0.08±0.59 g/dL, respectively (95% CI 0.06 to 0.93; p=0.026).

Conclusion: Daily iron supplementation of 10 mg/day is more effective than 30 mg weekly iron supplementation in improving iron status and hemoglobin level in the Thai infants.

Keywords: Anemia; Ferritin; Infants; Iron deficiency; Iron supplementation

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Iron is known to be an essential nutrient for the growing brain. Iron deficiency anemia (IDA) in infants can affect neurodevelopmental outcome and remains one of the major public health concerns worldwide, especially in developing countries[1-6]. In 2013, a large survey (SEANUTS) reported that prevalence of anemia in Thai children aged 6 months to 3 years was 26.0% in urban areas and 41.7% in rural areas[7]. According to another study in Thailand[8] between 2002 and 2003, 26.4% of healthy term infants were reported to have anemia, of which 14.3% were IDA. Although there were insufficient data of iron deficiency (ID) in infants, ID was assumed to be the most common cause of anemia in infants[9,10]. Infants' iron reserves are sufficient to maintain adequate iron state up until 4 to 6 months of age, therefore iron-rich complementary diet should be promoted afterward. Many nutritional studies from various countries found that infants' iron intakes were not adequate. Thus, iron fortification or supplementation should be endorsed as a national policy[10-13]. Universal screening for anemia and various methods of iron supplementation or fortification is recommended by The American Academy of Pediatrics (AAP), the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and the World Health Organization (WHO)[9,14,15]. In normal birth weight infants aged 6 to 12 months, iron supplementation of 12.5 mg/day is recommended by the International Nutritional Anemia Consultative Group (INACG)[16]. According to the WHO's 2016 guideline, daily iron supplementation of 10 to 12.5 mg/day for three

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consecutive months per year is recommended in children aged 6 to 23 months. If the prevalence of anemia is 20% to 40%, intermittent regimens of iron supplement could be considered[15]. In 2016, the prevalence of anemia in Thai children aged 6 to 59 months was 24.5%[17]. However, Thalassemia is prevalent in Thailand. There were concerns of iron overload if iron is generally supplemented to the Thai children. The Thai Guideline in Child Health Supervision suggests that infants 6 to 12 months of age should be screened for anemia once during the well-child visit. If anemia was present, the cause of anemia should be investigated and treated according to the cause. Otherwise, daily iron supplementation is recommended especially in infants with risks of ID or IDA. Risk factors associated with ID or IDA in infants included maternal anemia, poorly controlled diabetes during pregnancy, multiple gestation, early cord clamping, history of prematurity, low birth weight, exclusive breastfeeding beyond four months of age without iron supplementation, and iron-poor complementary diets[2,6,14,18,19]. Currently, intermittent iron supplementation of 12.5 mg once a week has been endorsed as another practical method of IDA prevention for Thai children aged 6 to 23 months[20]. According to various studies comparing daily and intermittent iron supplementation, the outcome of anemia, ID, or IDA prevention among the intermittent groups appeared promising[21-26]. The weekly regimen was intended to increase the medication adherence. Previous studies have compared intermittent regimen of 25 to 60 mg/week with daily regimen of 50 to 210 mg/week[22-26]. Nevertheless, the iron dosage supplemented in Thai infants of 12.5 mg/week, was much lower than the WHO recommendation of 10 mg/day for a total of 70 mg/week. Even intermittent doses of higher than 25 mg/week seemed not to be superior to the standard daily dose[23,25,26]. The effectiveness of the current intermittent regimen is uncertain and likely to be ineffective. A proportionate intermittent dose comparing with the standard daily dose should be further investigated.

The present study aimed to evaluate the effectiveness of weekly iron supplementation compared with daily supplementation in improving the iron status in Thai infants. The secondary objective was to compare the hematological status and side effects between groups. The present study weekly dose of 30 mg/week was initiated to maximize the single iron dose that would not be toxic to infants or not more than 6 mg/kg/day, and not less than the evident doses. Standard recommendation of 10 mg/day is represented as the controlled group.

Materials and Methods

Definitions

The terms and cut off values used in the present study were as follows, exclusive breastfeeding (EBF) with breast milk is the only or major source of milk during the first six months of life, anemia is hemoglobin (Hb) of less than 11 g/dL and hematocrit (Hct) is less than 33%, ID is serum ferritin (SF) less than 12 ng/mL, and IDA was defined when anemia and iron deficiency are both present[9,15].

Study design and participants

A single blind randomized controlled trial was conducted between May 2019 and November 2020 in Burapha University Hospital in Chonburi, Thailand. The Burapha University Institutional Review Board approved the present study (ethics code: 42/2562). The study adhered to the consolidated standards of reporting trials (CONSORT) statements. The CONSORT flow diagram of participant's enrollment is shown in Figure 1. The study was registered at the Thai Clinical Trials Registry (code: TCTR20191107001).

Healthy 6-month-old infants attending the Well Child Clinic at Burapha University Hospital were voluntarily enrolled to the present study. Only infants who met the following criteria were considered eligible, 1) singleton birth, 2) gestational age more than 37 weeks and birth weight more than 2,500 g, 3) no history of serious perinatal complication including cardiopulmonary resuscitation or blood or exchange transfusion, 4) have not previously taken any iron supplementation or therapy, 5) no chronic disease such as malnutrition, hematologic, cardiologic, pulmonologic, neurologic, and liver diseases. Eligible infants were screened for anemia by Hct screening as a routine well-child practice. Infants who were anemic with an Hct of less than 33% were excluded from the study. At the enrollment, information about the aim of study was provided to the parents. A written informed consent was obtained from parents who agreed to participate. Baseline characteristics including gestational age, birth weight, gender, weight, length, dietary intake, and perinatal and pregnancy complications were obtained. The determined dietary intake included breast milk, infant formula, and common Thai iron-rich complementary food, which included meat, liver, and yolk. Caregivers were advised to provide iron-rich complementary diets to their infants.

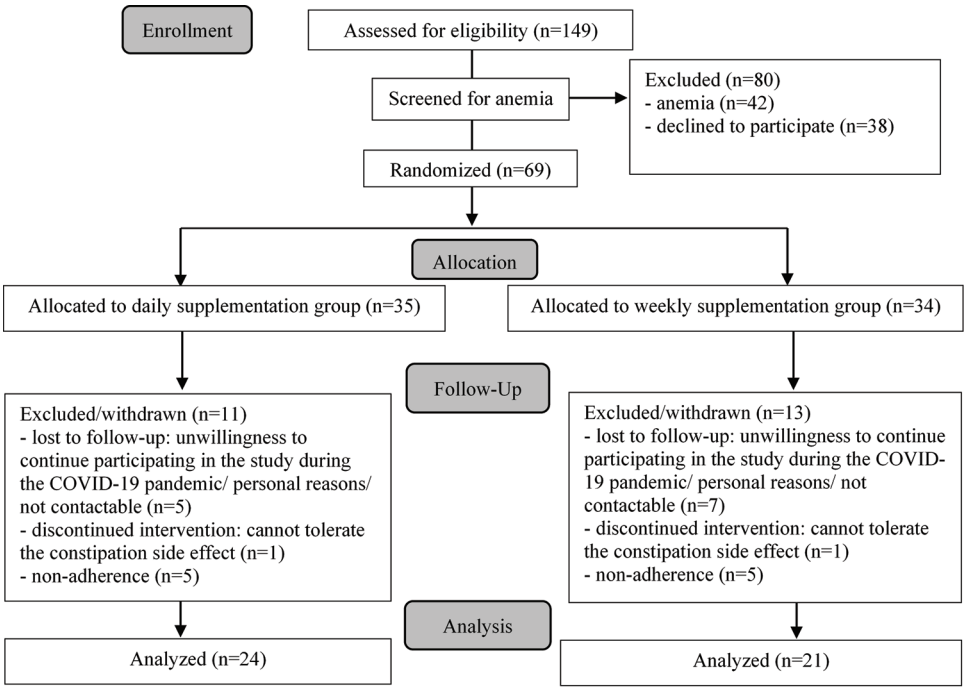

Figure 1. CONSORT flow diagram of participant enrollment.

Participants were randomized using a computer-generated randomization code. Allocation was concealed in opaque envelopes and numbered to mask the randomization code. The daily or weekly assignment was sealed accordingly. Envelopes were opened by research assistants only after the infant was sequentially enrolled by the investigators. All instructions were given by research assistants to blind the investigators from the allocation. Participants were distributed into two groups, one receiving a daily elemental iron 10 mg/day and the other receiving a weekly elemental iron of 30 mg/week iron supplementation. The given iron supplement was a commercially available formula of iron (III) hydroxide polymaltose complex (Eurofer®-Iron, Osoth Inter Laboratories, Chonburi, Thailand). The caregivers were instructed to give the iron supplements to their infants one hour before breakfast for six months as 1 mL every day in the daily group and 3 ml every Sunday in the weekly group, and record the dose taken or missed, side effects and any infection that occurred in the calendar booklet provided. If the daily dose was missed, the iron supplement should be taken as soon as they remember within the same day. If the weekly dose was missed, the iron supplement should be administered within the same week. Apart from that, it should be recorded as a missed dose.

The average daily dietary intake was collected every three months by phone or during well-child visits at 9 months old and 12 months old. Portion sizes were estimated using tablespoons and sample pictures. Caregivers were asked to recall the daily average food monthly. Food intake data were converted into iron intakes using the Thai Food Composition Database, Online version 2 (Institute of Nutrition, Mahidol University)[27]. Commercial infant formula available in Thailand contains iron 0.55 to 1.2 mg/dL. Conversion of 1 dL of infant formula to 0.8 mg of elemental iron was applied.

Venous blood sampling for complete blood count (CBC) and SF was collected from infants aged 6 and 12 months. If there were any recent infection of the participants, the blood sampling would be postponed for one week to prevent a falsely high SF. CBC was performed by automated cell counter (CAL 8000, Mindray, China). SF was measured by electrochemiluminescence (ECLIA) method (Cobas® pro 801, Roche, Germany).

A follow-up evaluation was scheduled at 12 months of age. The calendar booklets were collected back to the investigators. Side effects, any infection occurred, and adherence were checked. Non-adherent as lower than 80% participants were withdrawn from the analysis. The primary outcome was the change in SF level from the beginning. The secondary outcome was the changes in CBC and side effects occurred.

Table 1. Comparison of demographic features between studied groups

Demographic features	Daily (n=24); mean±SD	Weekly (n=21); mean±SD	p-value
Sex; n (%)			0.841†
Male	13 (54.2)	12 (57.1)	
Female	11 (45.8)	9 (42.9)	
Birth weight (g)	3,107±440	3,105±319	0.987‡
Gestational age (weeks)	38.75±1.15	38.43±1.12	0.350‡
EBF; n (%)	15 (62.5)	8 (38.1)	0.102†
Average iron intake (mg/day)			
Infant formula; median(IQR)	6.38 (1.50, 7.94)	6.00 (0.00, 8.63)	0.604§
Complementary food	2.77±1.39	2.61±1.18	0.672‡
Weight (kg)			
Age 6 months	7.89±1.06	7.71±0.81	0.530‡
Age 12 months	9.80±1.54	9.50±1.33	0.498‡
Length (cm)			
Age 6 months	69.42±2.90	69.17±3.26	0.787‡
Age 12 months	75.50±3.05	74.93±2.58	0.505‡

EBF=exclusively breast-fed infants; IQR=interquartile range; SD=standard deviation

† Chi-square test, ‡ Independent sample t-test, § Mann-Whitney U test

Sample size and statistical analysis

Assuming that weekly iron supplementation would be as effective as daily iron supplementation. The formula for non-inferiority design was used. The sample size required to be able to distinguish a difference between groups in the ferritin level was 25 in each group, defined the significant level at 0.05 and power of test 80%[24]. Most infants in the well child clinic were child of migrant workers and a high dropout rate was presumed. Assuming a dropout rate of 40%, 70 participants was used in the present study. Results were analyzed using IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA). Analysis of continuous data with a normal distribution was conducted by independent sample t-test, while non-normal distribution was conducted by Mann-Whitney U test. Categorical data was analyzed by chi-square test or Fisher's exact test where applicable.

Results

One hundred forty-nine six-month-old infants were eligible and screened for anemia. Eighty infants were excluded as 42 infants were anemic and 38 declined to participate. Sixty-nine infants were randomized into daily group (n=35) and weekly group (n=34). The enrollment ended ahead of schedule because of the difficulty during the COVID-19 pandemic. Fourteen participants did not return for follow up or discontinued the intervention. Ten participants were withdrawn from the analysis due to non-adherent to medication. Forty-five participants remained for analyses with 24 in the daily group and 21 in the weekly group.

Baseline characteristics including gender, birth weight, gestational age, percentage of exclusive breast-fed infants, average iron intake, weight, and length of both baseline and final point were not different between groups (Table 1).

The baseline, at 6 months, and the final, at 12 months, iron status and hematological variables (Hb, Hct, and SF) were not significantly different between groups except for the initial mean corpuscular volume (MCV). The initial mean MCV of the weekly group was significantly larger than the daily group at 75.80±4.83 versus 71.62±7.85 fL (p=0.04). The average differences of SF after six-month period of iron supplementation were 10.85 (–13.19, 34.49) ng/mL in the daily group and –9.31 (–23.86, –2.30) ng/mL in the weekly group (p=0.012). The average differences of Hb were 0.58±0.82 g/dL in the daily group and 0.08±0.59 g/dL in the weekly group (95% CI 0.06 to 0.93; p=0.026). The difference of Hct and MCV were not statistically significant (Table 2).

Numbers of infants with ID were observed at both baseline and final point. Initially, at 6 months old, 29.2% of the daily group and 9.5% of the weekly group were found to have ID. When the infants were followed at age 12 months old, the frequency of iron-

Table 2. Comparison of serum ferritin and hematological variables between studied groups

Variables	Daily (n=24); mean±SD	Weekly (n=21); mean±SD	p-value	95% CI
Age 6 months				
Hb (g/dL)	11.47±0.68	11.63±0.48	0.367†	−0.52 to 0.19
Hct (%)	34.79±1.93	34.90±1.37	0.825†	−1.14 to 0.91
MCV (fL)	71.62±7.85	75.80±4.83	0.040†	−8.17 to −0.19
Ferritin (ng/mL)	32.95±26.68	42.13±27.92	0.266†	−25.61 to 7.25
Age 12 months				
Hb (g/dL)	12.05±0.91	11.71±0.76	0.195†	−0.18 to 0.84
Hct (%)	36.29±2.39	35.42±2.04	0.202†	−0.48 to 2.21
MCV (fL)	74.84±8.03	77.41±4.98	0.212†	−6.66 to 1.52
Ferritin (ng/mL); median (IQR)	34.36 (21.61, 62.98)	26.47 (11.48, 38.53)	0.097‡	-
Differences				
Hb (g/dL)	0.58±0.82	0.08±0.59	0.026†	0.06 to 0.93
Hct (%); median (IQR)	1.00 (1.00, 3.00)	1.00 (−1.00, 2.00)	0.114‡	-
MCV (fL); median (IQR)	2.50 (0.73, 4.60)	1.70 (0.75, 2.65)	0.237‡	-
Ferritin (ng/mL); median (IQR)	10.85 (−13.19, 34.49)	−9.31 (−23.86, −2.30)	0.012‡	-

CI=confidence interval; Hb=hemoglobin; Hct=hematocrit; MCV=mean corpuscular volume; IQR=interquartile range; SD=standard deviation

† Independent sample t-test, ‡ Mann-Whitney U test

Table 3. Frequency of infants who reported side effects during 6 months of iron supplementation

Side effect	Daily (n=30); n (%)	Weekly (n=29); n (%)	p-value
Total	7 (23.3)	9 (31.0)	0.506†
Spit/vomit	5 (16.7)	8 (27.6)	
Constipation	2 (6.7)	1 (3.4)	

† Chi-square test

deficient infants decreased to 12.5% in the daily group but increased to 33.3% in the weekly group.

The frequency of side effects between groups are compared in Table 3. The data were collected and analyzed from all the contactable participants, which was 30 for the daily group and 29 for the weekly group. Seven (23.3%) infants in the daily group compared with nine (31.0%) infants in the weekly group reported side effects related to the iron supplements. The most serious side effect was constipation resulting in two participants withdrawing from the study with one from each group. Other side effects were vomiting or spitting, maybe due to unfavorable taste, which affected the adherence of the participants. The total side effect rate was not different between groups (p=0.506). Ten participants, with five infants from each group, were non-adherent to medication. Among the non-adherent participants, four infants from the daily group and two infants from the weekly group did not experience any side effect.

Discussion

In the hypothesis of the present study, daily and weekly iron supplementations are equally effective in improving the infants' iron status. However, the present study has shown that only daily iron supplementation is effective in improving the iron status, while weekly iron supplementation is not. The weekly group initially tended to have a better iron status than the daily group, with a higher average SF level. After six months of supplementation, the average SF level in the weekly group decreased but the average SF level in the daily group increased. In addition, the observation of infants with ID has shown that the weekly-group infants seemed to subsequently develop ID more than the daily-group. The present study result of intermittent iron supplementation has not been observed in the previous studies[22,24-26]. Most of the iron-deficient infants were exclusively breast-fed and tended to continue with breast milk as the major formula through the age of 12 months. This could possibly support that weekly iron supplementation of 30 mg is not enough to maintain iron status in infants who were breast-fed beyond six months.

The hematological variables of both groups were compared. The Hb level of both groups have shown improvement, whilst the daily group improved more than the weekly group significantly. The baseline MCV of the weekly group were significantly larger

than the daily group. However, at the end point, the MCV in terms of size and difference between groups were not significantly different. This might be due to the red blood cells of the weekly group having reached their maximal size, weekly supplementation was less effective, or the infants had Thalassemia trait. Therefore, daily iron supplementation could somehow improve the MCV parameters better than in the weekly group, although not statistically significant.

The comparison between the present study and the previous studies of intermittent and daily iron supplementation were simplified and are shown in Table 4. There were variations of situation and limitation among studies. Some of the studies had more than two arms but this table was simplified to compare with the present study. The previous studies' population ranged from four to 60 months, the duration of iron supplementation ranged from two to six months and the iron formulation used were ferrous sulfate. Compared to the previous studies, intermittent iron supplementation may not differ from daily supplementation in terms of preventing ID, IDA, or anemia[23-25], increasing Hb level[22-26], and increasing ferritin level[22,25,26]. Apart from these studies, Ermis et al[24] demonstrated a higher SF increment of the intermittent group than the daily group as the total iron dose of both groups in the study were equal. However, the iron cumulative dose per week of the previous reports were mostly higher than the present study. Some of them were similar between groups, which could be the reason why intermittent and daily supplementation outcome were not significantly different. The present study was carried out with a longer duration of iron supplementation, which may be another additional factor. However, the general outcomes of the previous studies were similar to the present study of which the more iron supplemented, the better improvement of iron or hematological status. Further studies comparing a higher dose of intermittent supplementation with the standard recommendation dose could be evaluated.

The limitations of the present study were the dietary intake interview that was recalled every three months and the average iron intake during six to twelve months from complementary food may be underestimated. Only common Thai iron-rich complementary food, not the commercial food intake was calculated as the iron intake from food. The results have shown that the main source of iron intake in six to twelve months infants was from infant formula rather than complementary food. Another important limitation is the unexpected high drop-out

Table 4. The comparison of the present study with previous studies of intermittent and daily iron supplementation†

Articles	Country	Age (month)	Iron formulation	Duration of iron supp (month)	Intervention (Intermittent group)				Control (Daily group)				Outcome (intervention vs. control)			
					n	Baseline Hb±SD (g/dL)	Admin	Total dose (mg/week)	n	Baseline Hb±SD (g/dL)	Admin	Total dose (mg/week)	Incidence of ID/IDA/ anemia (%)	Mean Hb diff (g/dL)	Mean ferritin diff (ng/mL)	Mean MCV diff (fL)
Present study	Thailand	6	Iron polymaltose	6	21	11.6±0.48	30 mg/week (weekly)	30	24	11.5±0.68	10 mg/day	70	ID/IDA 33 vs. 12.5	0.08 vs. 0.58 (p=0.026)	−13.05 vs. 8.78 (p=0.012)	1.6 vs. 3.2 (p=0.237)
Khademloo et al. 2009[22]	Iran	6 to 24	Ferrous sulfate	3	50	11.9±0.68	30 drops/week (weekly)	N/A	50	11.7±0.53	15 drops/day	N/A	N/A	0.35 vs. 0.59 (p=0.14)	2.8 vs. 0.1 (p=0.2)	N/A
Engstrom et al. 2008[23]	Brazil	6	Ferrous sulfate	6	150	N/A	25 mg/week (weekly)	25	147	N/A	12.5 mg/day	87.5	Anemia 60.5 vs. 50.7 (p=0.124)	0.29 vs. 0.58 (p=0.103)	N/A	N/A
Ermis et al. 2002[24]	Turkey	5	Ferrous sulfate	4	27	11.0±0.33	7 mg/kg/week (EOD)	49.7 (avg weight 7.1 kg)	28	11.0±0.36	7.1 mg/day (1 mg/kg/day)	49.7 (avg weight 7.1 kg)	ID 0 vs. 0	0.6 vs. 0.6 (p=0.92)	15.8 vs. 9.2 (p=0.038)	2.1 vs. 2.0 (p=1)
Yurdakok et al. 2004[25]	Turkey	4 (EBF)	Ferrous sulfate	3	22	11.4±0.7	7 mg/kg/week (weekly)	7 mg/kg/week	23	11.1±0.4	1 mg/kg/day	7 mg/kg/week	ID/IDA 13.6 vs. 26.0 (NS)	0.2 vs. 0.3 (NS)	17.6 vs. 14.2 (NS)	−0.9 vs. −1.1 (NS)
Schultink et al. 1995[26]	Indonesia	24 to 60	Ferrous sulfate	2	32	10.4±1.1	60 mg/week (2 day/week)	60	33	10.8±1.1	30 mg/day	210	N/A	0.7 vs. 1.3 (NS)	18.0 vs. 25.8 (NS)	N/A

Admin=administration; avg=average; diff=difference; EBF=exclusively breast-fed; EOD=every other day; Hb=hemoglobin; ID=iron deficiency; IDA=iron deficiency anemia; MCV=mean corpuscular volume; supp=supplementation; NS=non-significant; N/A=not applicable

† Some of the studies had more than 2 arms but this table was simplified to compare with the present study

rate during COVID-19 pandemic. This limitation resulted in the power of test to be less than calculated and a possible selection bias such as volunteer bias.

During enrollment period, the authors found that 28.2% of eligible infants were anemic. The prevalence of anemia in the present study tended to be similar to the previous reports in Thailand for the past 10 to 20 years[7,8,17]. Future studies should aim to ameliorate the IDA in infancy, which is the critical period of neurodevelopment.

Conclusion

Daily iron supplementation of 10 mg/day is more effective than 30 mg weekly iron supplementation in improving iron status and Hb level in the Thai infants. To prevent iron deficiency, it is recommended to provide daily iron supplementation according to the WHO recommendation for infants aged 6 to 12 months.

What is already known on this topic?

According to the WHO's 2016 guideline, daily iron supplementation of 10 to 12.5 mg/day for three consecutive months per year is recommended in children aged 6 to 23 months. The prevalence of anemia in Thai children aged 6 to 59 months for the past ten years, between 2009 and 2019, was around 24% to 25%, for which intermittent regimen of iron supplement can be considered. Current policy in Thailand is to provide iron supplementation of 12.5 mg once a week to prevent IDA in children aged 6 to 23 months.

What this study adds?

The findings support that daily iron supplementation regimen should be considered to prevent iron deficiency in the Thai infants. Weekly iron supplementation of 30 mg is inadequate to prevent iron deficiency in infants.

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Author's contributions

Pattrakornkul N, Tangjaturonrasme S, and Yampratoom R designed the study. Pattrakornkul N, Ngamcherdtrakul P, Kriangburapa W, and Yampratoom R collected and analyzed the data. Pattrakornkul N performed the statistical analysis and drafted the manuscript. Yampratoom R critically reviewed the manuscript and supervised the whole study process. All authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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