A Randomized Controlled Trial of Daily and Weekly Iron Supplementations for Improving Iron Status in the Infants

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Abstract

Background: Iron deficiency anemia screening and iron supplementation in infants aged 6-12 months are recommended in the Guideline in Child Health Supervision. This study aims to evaluate the effectiveness of weekly iron supplementation compared with daily supplementation in improving the iron status in infants.

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 six-month-old healthy infants were randomized to receive either 10 mg Fe/day (daily group) or 30 mg Fe/week (weekly group). Forty-five infants (daily group; n = 24 and weekly group; n = 21) completed the intervention. After the six-month period of iron supplementation, the mean differences of serum ferritin in the daily and the weekly group were 8.78±37.21 and -13.05 ±17.53 ng/mL, respectively (95%CI: 4.54, 39.12; P=0.015). The mean 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, 0.93; P=0.026). Daily supplementation could prevent iron deficiency more than weekly supplementation significantly (P=0.029), particularly in the exclusive breastfeeding subgroup (P=0.032).

Conclusions: Daily iron supplementation is more effective than weekly iron supplementation in improving iron status and hemoglobin level in infants, especially in the exclusively breast-feds.

Trial registration: TCTR20191107001, November 7th, 2019. Retrospectively registered, http://www.thaiclinicaltrials.org

Background

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] during 2002-2003, 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 for 4-6 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/supplementation should be endorsed as a national policy [10-13]. Universal screening for anemia and various methods of iron supplementation/fortification is recommended by The American Academy of Pediatrics (AAP), European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and World Health Organization (WHO) [9, 14-15]. In normal birth weight infants aged 6-12 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 10-12.5 mg/day for three consecutive months per year is recommended in children aged 6–23 months. If the prevalence of anemia is 20-40%, intermittent regimens of iron supplement can be considered. However, Thalassemia is prevalent in Thailand. There were concerns of iron overload if iron is generally supplemented to the Thai children. *Thai Guideline in Child Health Supervision* suggests that infants 6-12 months of age should be screened for anemia once during the well-child visit. If anemia is 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/IDA. Risk factors associated with ID/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 4 months of age without iron supplementation, and iron-poor complementary diets [2, 6, 14, 17-18]. 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 6-23 months [19]. According to various studies comparing daily and intermittent iron supplementation, the outcome of anemia/ID/IDA prevention among the intermittent groups appeared promising [20-25]. The weekly regimen was intended to increase the medication adherence. Nevertheless, the iron dosage supplemented in Thai infants was much lower than the WHO recommendation (12.5 mg/week vs 12.5 mg/day) and previous studies [20-25]. The effectiveness of the current regimen is uncertain.

This study aims to evaluate the effectiveness of weekly iron supplementation compared with daily supplementation in improving the iron status in Thai infants. The secondary objective is to compare the hematological status and side effects between groups. Our weekly dose of 30 mg/week was initiated according to maximizing the single iron dose that would not be toxic to infants. Standard recommendation of 10 mg/day is represented as the controlled group.

Methods

Definitions

The terms and cut off values used in this study are as follows: exclusive breastfeeding (EBF): breast milk is the only/major source of milk during the first six months of life; anemia: hemoglobin (Hb) less than 11 g/dL and hematocrit (Hct) less than 33%; iron deficiency (ID): serum ferritin (SF) less than 12 ng/mL, and iron deficiency anemia (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 from May 2019 to November 2020 in Burapha University Hospital in Chonburi, Thailand. The Burapha University Institutional Review Board approved this 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 are shown in Figure 1. The study was registered at the Thai Clinical Trials Registry (code: TCTR20191107001).

Healthy 6-month-old infants who attended the Well Child Clinic at Burapha University Hospital were voluntarily enrolled to the 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/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 (Hct <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/pregnancy complications were obtained. The determined dietary intake included breast milk, infant formula, and common Thai iron-rich complementary food (meat, liver, and yolk). Caregivers were advised to provide iron-rich complementary diets to their children.

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 daily (elemental iron 10 mg/day) and the other receiving weekly (elemental iron 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 1 hour before breakfast for 6 months (1 ml every day in the daily group and 3 ml every Sunday in the weekly group) and record the dose taken/missed, side effects and any infection 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 Thai Food Composition Database, Online version 2 (Institute of Nutrition, Mahidol University) [26]. Commercial infant formula available in Thailand contains iron 0.55-1.2 mg/dL. Conversion of 1 dL of infant formula to 0.8 mg of elemental iron was applied.

Venous blood sampling for 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 1 week to prevent the 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 (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.

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]. Assuming a dropout rate of 40%, therefore a total of 70 participants was used in this study. Results were analyzed using SPSS Version 20.0. Analysis of continuous data with a normal distribution was conducted by independent sample *t*-test. Categorical data was analyzed by Chi-square test or Fisher's exact test where applicable.

Results

A total of 149 six-month-old infants were eligible and screened for anemia. Eighty infants were excluded (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 scheduled because of the difficulty during the COVID-19 pandemic. Fourteen participants lost to follow-up and/or discontinued the intervention. Ten participants were withdrawn from the analysis due to non-adherent to medication. There were 45 participants remaining to the analysis (daily group; n = 24 and weekly group; n = 21).

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

Table 1 Comparison of demographic features between studied groups

Demographic features	Daily (*n* = 24) mean ± SD	Weekly (*n* = 21) mean ± SD	*P* value
Gender, 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, wk	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	5.54 ± 3.85	5.04 ± 4.44	0.684 #
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

* Chi-square test

independent sample *t*-test

The baseline (aged 6 months) and final (aged 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 (75.80 ± 4.83 vs 71.62 ± 7.85 fL, *P* = 0.04). The mean difference of SF after six-month period of iron supplementation was 8.78 ± 37.21 ng/mL in the daily group and -13.05 ± 17.53 ng/mL in the weekly group (95%CI: 4.54, 39.12; *P* = 0.015). The mean difference of Hb was 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, 0.93; *P* = 0.026). The mean difference of Hct and MCV were not statistically significant (Table 2).

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 , 0.19
Hct, %	34.79 ±1.93	34.90 ± 1.37	0.825	-1.14 , 0.91
MCV, fL	71.62 ± 7.85	75.80 ± 4.83	**0.040**	-8.17 , -0.19
Ferritin, ng/mL	32.95 ± 26.68	42.13 ± 27.92	0.266	-25.61 , 7.25
Age 12 months				
Hb, g/dL	12.05 ± 0.91	11.71 ± 0.76	0.195	-0.18 , 0.84
Hct, %	36.29 ± 2.39	35.42 ± 2.04	0.202	-0.48 , 2.21
MCV, fL	74.84 ± 8.03	77.41 ± 4.98	0.212	-6.66 , 1.52
Ferritin, ng/mL	41.74 ± 28.47	29.08 ± 22.39	0.108	-2.91 , 28.21
Differences				
Hb, g/dL	+ 0.58 ± 0.82	+ 0.08 ± 0.59	**0.026**	0.06 , 0.93
Hct, %	+ 1.50 ± 2.00	+ 0.52 ± 1.99	0.109	-0.23 , 2.18
MCV, fL	+ 3.22 ± 3.74	+ 1.61 ± 1.29	0.058	-0.06 , 3.27
Ferritin, ng/mL	+ 8.78 ± 37.21	- 13.05 ± 17.53	**0.015**	4.54 , 39.12

CI confidence interval, *Hb* hemoglobin, *Hct* hematocrit, *MCV* mean corpuscular volume

[#] Independent sample *t*-test

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 number of iron-deficient infants decreased to 12.5% in the daily group but increased to 33.3% in the weekly group. The ID status change after iron supplementation were changed to categorical data by using the definition as follows: -1; the non-ID have changed to ID/IDA, +1; the ID have changed to non-ID and 0; the ID and non-ID remained unchanged. The results have shown that the weekly-group infants subsequently developed ID more than the daily-group. The daily-group infants also subsequently improved iron sufficiency more than the weekly-group significantly (*P* = 0.029). In the subgroup analysis (EBF vs non-EBF), ID status modification was statistically significant between daily and weekly groups only in the exclusively breast-fed subgroup (*P* = 0.032) (Table 3).

Table 3 Comparison of EBF infants and the association with iron deficiency status changes between studied groups

	Total, *n* (%)		EBF, *n* (%)		Non-EBF, *n* (%)	
ID status	Daily (*n* = 24)	Weekly (*n* = 21)	Daily (*n* = 15)	Weekly (*n* = 8)	Daily (*n* = 9)	Weekly (*n* = 13)
ID						
Age 6 months	7 (29.2%)	2 (9.5%)	7 (46.7%)	2 (25%)	0	0
Age 12 months	3 (12.5%)	7 (33.3%)	2 (13.3%)	5 (62.5%)	1 (11.1%)	2 (15.4%)
Status change [#] [-*n* , +*n*]	[-2 , +6]	[-5, +0]	[-1 , +6]	[-3 , +0]	[-1 , +0]	[-2 , +0]
P value *	**0.029**		**0.032**		1.000	

EBF exclusively breast-fed, *ID* iron deficiency

[#] Frequency of ID status change was reported as follows: -*n* the non-ID have changed to ID, +*n* the ID have changed to non-ID

* Chi-square test: *P* value of ID status changes between daily and weekly group

The frequency of side effects between groups were compared in Table 4. The data was collected and analyzed from all the contactable participants (daily group; *n* = 30 and weekly group; *n* = 29). Seven (23.3%) infants in the daily group compared with nine (31.0%) infants in the weekly group were reported with side effects related to the iron supplements. The most serious side effect was constipation resulting in two participants withdrawing from the study (one from each group). Other side effects were vomiting/spitting (reportedly due to unfavorable taste) which affected the adherence of the participants. The total side effect rate was not different between groups (*P* = 0.506).

Table 4 Frequency of infants who reported side effects during 6 months of iron supplementation

Side effect	Daily (*n* = 30)	Weekly (*n* = 29)	*P* value
Total, *n* (%)	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

Discussion

In the hypothesis of the study, daily and weekly iron supplementations are equally effective in improving the infants' iron status. However, this study has shown that only daily iron supplementation is effective in improving the iron status while weekly iron supplementation is not enough. The weekly group initially tended to have a better iron status than the daily group, according to the higher mean SF level and lower percentage of ID. After 6 months of weekly iron supplementation, there were decremental change of the SF level and frequency of iron-sufficient infants. In contrast, the SF level was increased and the frequency of iron-deficient infant was decreased in the daily group. This result of intermittent iron supplementation has not been observed in previous studies [21,23-25]. 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. 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. During subgroup analysis, we found that most of the iron-deficient infants were exclusively breast-fed which tended to continue with breast milk as the major formula through the age of 12 months. This may conclude that weekly iron supplementation of 30 mg is not enough to maintain the iron status in the infants who were breast-fed beyond 6 months.

The comparison between this study and previous studies of intermittent and daily iron supplementation were simplified and shown in Table 5. (There were variations of situation and limitation among studies. Some of the studies had more than 2 arms but this table was simplified to compare with this study.) The previous studies' population ranged from 4 to 60 months, the duration of iron supplementation ranged from 2 to 6 months and the iron formulation used were ferrous sulfate. Compared to previous studies, intermittent iron supplementation may not differ from daily supplementation in terms of preventing ID/IDA/anemia [22-24], increasing Hb level [21-25], and increasing ferritin level [21, 24-25]. Apart from these studies, Ermis et al [23] demonstrated a higher SF increment of the intermittent group than the daily group (the total iron dose of both groups in this study were equal). However, the iron cumulative dose per week of previous reports were mostly higher than our study. Some of them were similar between groups which could be the reason why intermittent and daily supplementation outcome were not significantly different. This study was carried out with a longer duration of iron supplementation which may be another additional factor. However, the general outcomes of previous studies were similar to this study of which the more iron supplemented the better improvement of iron/hematological status. Further studies comparing a higher dose of intermittent supplementation with the standard recommendation dose could be evaluated.

The limitations of this study were the dietary intake interview which was recalled every 3 months and the average iron intake during 6-12 months from complementary food may be underestimated. Only the common Thai iron-rich complementary food (not the commercial) intake was calculated as the iron intake from food. The results have shown that the main source of iron intake in 6-12 months infants was from infant formula rather than complementary food.

During enrollment period, we found that 28.2% of eligible infants were anemic. The prevalence of anemia in this study tended to be similar to previous reports in Thailand for the past 10-20 years [7-8, 27]. Future studies should be aiming to ameliorate IDA in infancy which is the critical period of neurodevelopment.

Table 5 The comparison of this study with previous studies of intermittent and daily iron supplementation*

Articles	Country	Age (mon)	Iron formulation	Duration of iron supp	Intervention (Intermittent group)				Control (Daily group)			
					n	Baseline Hb ± SD (g/dL)	Admin	Total dose (mg/week)	*n*	Baseline Hb ± SD (g/dL)	Admin	T (r
This study	Thailand	6	iron polymaltose	6 mon	21	11.6±0.48	30 mg/wk	30	24	11.5±0.68	10 mg/d	7
Khademloo M et al. 2009 [21]	Iran	6-24	ferrous sulfate	12 wk	50	11.9±0.68	30 drops/wk	N/A	50	11.7±0.53	15 drops/d	N
Engstrom EM et al. 2008 [22]	Brazil	6	ferrous sulfate	24 wk	150	N/A	25 mg/wk	25	147	N/A	12.5 mg/d	8
Ermis B et al. 2002 [23]	Turkey	5	ferrous sulfate	4 mon	27	11.0±0.33	14.2 mg/EOD (2mg/kg/EOD)	49.7 (Avg wt 7.1 kg)	28	11.0±0.36	7.1 mg/d (1mg/kg/d)	4 (A 7
Yurdakok K et al. 2004 [24]	Turkey	4 (EBF)	ferrous sulfate	3 mon	22	11.4±0.7	7 mg/kg/wk	7 mg/kg/wk	23	11.1±0.4	1 mg/kg/d	7 m
Schultink W et al. 1995 [25]	Indonesia	24-60	ferrous sulfate	2 mon	32	10.4±1.1	30 mg x 2 d/wk	60	33	10.8±1.1	30 mg/d	2

admin administration, *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 this study.

Conclusions

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

Abbreviations

EBF: Exclusive breastfeeding; Hct: hematocrit; Hb: hemoglobin; ID: Iron deficiency; IDA: Iron deficiency anemia; MCV: Mean corpuscular volume; SF: serum ferritin; SPSS: Statistical Package for Social Sciences; WHO: World Health Organization

Declarations

Ethics approval and consent to participate

The study was approved by the Burapha University Institutional Review Board (ethics code: 42/2562). Written informed consent was obtained from all parents of the participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NP and RY: Conception or design of work, acquisition of data, analysis or interpretation of data, drafting the manuscript, accountable for all aspects of work. NP edited the final manuscript. PN and WK: Conception or design of work, acquisition of data, revising the manuscript, accountable for all aspects of work. ST: Conception and design of work, revising the manuscript, accountable for all aspects of work. All authors have read and approved the manuscript.

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Figures

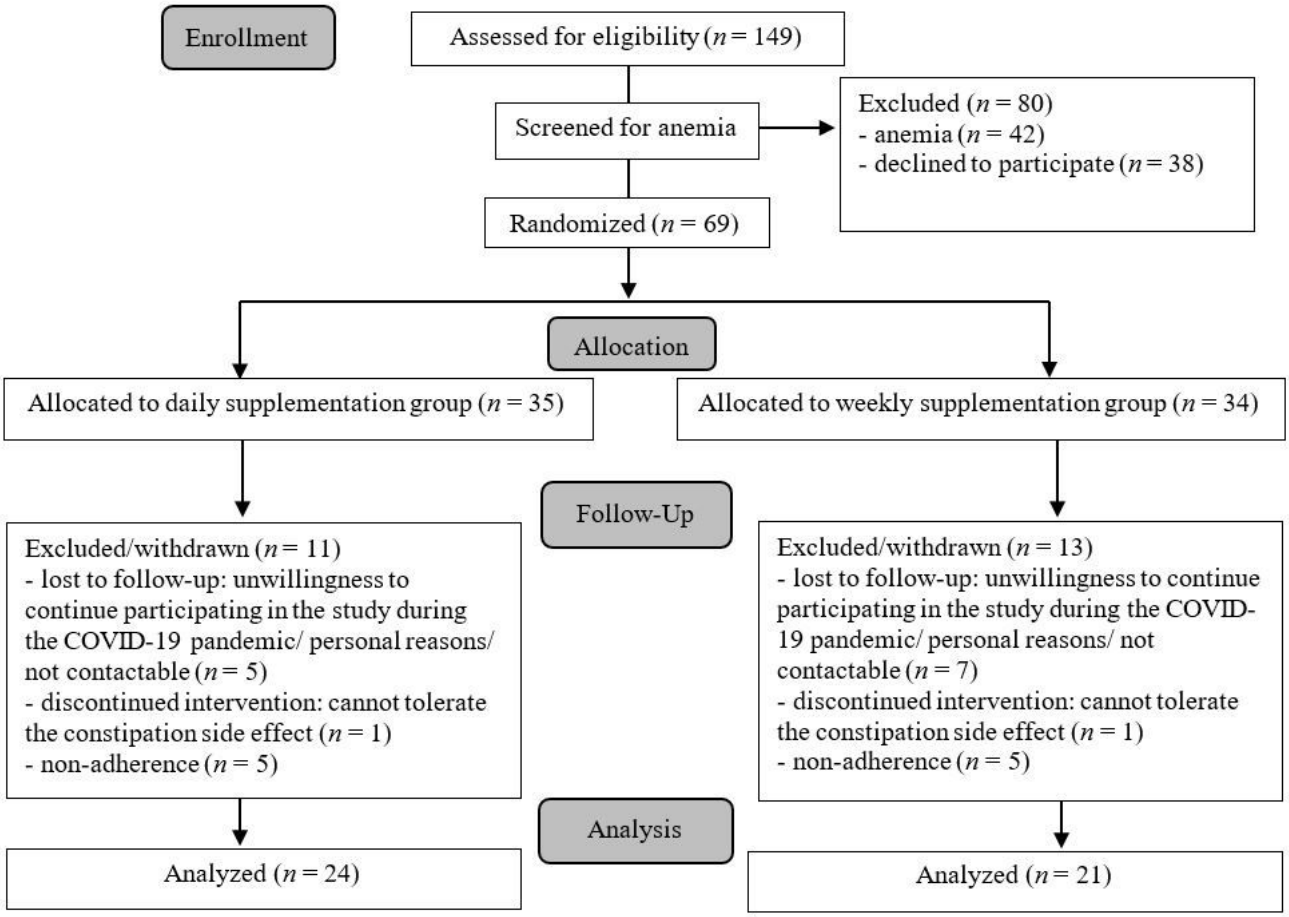

Figure 1

CONSORT flow diagram of participant enrollment

Supplementary Files

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- CONSORT2010Checklist.doc