

Comparative Efficacy of Ferrous, Ferric and Liposomal Iron Preparations for Prophylaxis in Infants

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ABSTRACT

Objective: This study aimed to assess the efficacy of different oral iron preparations prescribed for prevention of iron deficiency anemia in healthy infants.

Methods: This retrospective study enrolled infants aged between 6 and 12 months who were initiated on iron prophylaxis at four months of age. Enrolled children consistently used specific iron preparations (ferrous, ferric or liposomal iron) and had their complete blood counts and serum ferritin levels assessed within the 6-12 month timeframe. Blood values and iron prophylaxis type (ferrous (Fe⁺²), ferric (Fe⁺³), liposomal iron) were recorded. *Chi*-square test was used to compare the hemoglobin and ferritin levels between groups. Univariate and multivariate regression analyses assessed the risk of anemia.

Results: The study included 371 children (ferrous sulphate - 60, iron hydroxide-polymaltose complex - 137 and liposomal ferric pyrophosphate - 174) with a mean (SD) age 9.1 (1.3) mo. Iron deficiency in different groups were: liposomal iron (46.0%), ferric iron (44.5%), and ferrous iron (5.0%). Mean (SD) serum ferritin levels (µg/L) were higher in the ferrous group [30.1 (10.8)] compared to infants receiving ferric [17.6 (14.50)] and liposomal iron [15.4 (12.1)] ($P < 0.001$). Mean (SD) hemoglobin levels (g/dL) were significantly higher in the ferrous group [12.4 (0.8)] compared to ferric [11.9 (1.1)] and liposomal iron group [12.0 (1.1)]; $P = 0.008$. Multiple regression analysis showed that ferrous group was associated with a lower risk of iron deficiency [OR (95% CI) 0.04 (0.01-0.15), $P < 0.001$].

Conclusion: Ferrous iron demonstrated superior efficacy compared to ferric and liposomal iron. Further studies are needed to establish alternative iron preparations in children.

Keywords: *Child, Ferrous, Ferric, Iron deficiency anemia, Liposomal iron, Prophylaxis*

INTRODUCTION

Iron deficiency anemia (IDA) is a significant health concern affecting a considerable number of children worldwide particularly between the age of 4 and 23 months [1].

Breast milk offers excellent nutrition to meet the infants' iron needs for the first 4-6 months but does not suffice, as they grow. The introduction of iron-rich foods during complementary feeding by 6 months becomes important [2,3]. In Turkey, the Ministry of Health has instituted a National Health Program since 2004 targeting iron deficiency in infants aged 4-12 months [4]. Iron preparations were initially provided in a ferrous form that was replaced with a ferric form over the last eleven years to overcome the short supply. However, concerns of efficacy and associated side effects persist [5,6]. Ferric iron is generally better tolerated with reduced gastrointestinal side effects [7,8]. In response to challenges in administering traditional iron preparations, alternative options like liposomal iron products have emerged [9,10]. Liposomal iron, composed of iron salts within a phospholipid membrane, shields iron from gastric acid damage and aids its passage to the small intestine. This facilitates iron absorption by M cells in the intestine, to be taken up by macrophages through endocytosis and transported intact to hepatocytes via the lymphatic system. This protective

mechanism ensures iron stability, preventing degradation or inactivation in the stomach, and diminishes gastrointestinal side effects.

Addressing iron deficiency and anemia in infants in the initial two years is pivotal for ensuring their optimal growth and development. However, there is limited evidence on the comparison of traditional and newer iron products used for prophylaxis in infants. The primary aim of this study was to compare the effectiveness of ferrous, ferric, and liposomal iron supplements in iron prophylaxis in healthy infants aged 6-12 months who were initiated iron prophylaxis starting at four months of age.

METHODS

This retrospective study was conducted at Baskent University Hospital and Ankara Bilkent City Hospital, focused on patients who attended the general pediatric clinic for well-child visit. The study received ethical approval from the respective hospitals' ethics committees.

Healthy infants delivered at term gestation (gestational age ≥ 37 weeks) aged 6-12 months who had undergone routine blood tests between 6-12 months of age were eligible for enrolment. We included infants who had been initiated on one of three oral iron preparations (ferrous sulphate, iron hydroxide-polymaltose complex, liposomal ferric pyrophosphate) at 4 months and had received regular iron prophylaxis, and for whom records of hospital visits including information about laboratory tests and specific iron preparations prescribed were available. Iron was prescribed in a dose of 1 mg/kg/day of elemental iron for all the three drug formulations. Infants who had symptoms of infection at the time of the visit, or had raised levels of C-reactive protein (CRP) (> 5 mg/L) or leukocytosis were excluded. Infants with a prior diagnosis of iron deficiency anemia (IDA) and/or chronic diseases were further excluded from the study.

The demographic information (age, gender, feeding patterns, medical history) and laboratory investigations like hemoglobin (Hb) levels, serum ferritin, hematocrit (Hct), red blood cell distribution width (RDW), and mean corpuscular volume (MCV) were obtained from records. Pediatric phlebotomists at Baskent University Hospital and Ankara Bilkent City Hospital collected venous blood samples from patients for hemogram and ferritin analysis. The hemogram samples were drawn into EDTA-containing vacutainer tubes and analyzed using the Alinity HQ autoanalyzer at Baskent University Hospital, and the ADVIA 2120 Hematology System at Ankara Bilkent City Hospital. Serum ferritin levels were measured using the Alinity I Ferritin analyzer at Baskent University Hospital and with the Cobas-e 601 analyzer at Ankara Bilkent City Hospital.

Iron deficiency and iron deficiency anemia were determined using criteria laid by the World Health Organization (WHO) [11,12]. Iron deficiency was defined as ferritin concentrations below 12 $\mu\text{g/L}$. Iron-deficiency anemia was identified by both hemoglobin levels below 11 g/dL and ferritin concentrations below 12 $\mu\text{g/L}$. Infants were categorized as exclusively breastfed, breastfed with formula supplementation, or solely formula-fed to assess the nutritional status in the first 6 months.

The study utilized the growth curve references for Turkish children to analyze weight and height data [13]. The participant data was categorized into specific percentiles, ranging from below the 3rd percentile to

above the 97th percentile. Regression analysis was conducted to determine whether children's weight and height fell within the normal range (3rd and 97th percentiles) based on the type of iron preparations used.

Statistical Analysis: Data were analyzed using IBM SPSS software package version 20.0 (IBM Corp). Descriptive statistics, such as means, standard deviations, and frequencies were calculated for the study variables. Normal distribution of the variables was checked using the Kolmogorov-Smirnov test. Categorical variables were compared between groups using the *Chi* square test, and in cases where more than 20% of the cells had an expected count of less than 5, Fisher's exact test or Monte-Carlo correction was employed. ANOVA test was utilized for comparing more than two groups with normally distributed quantitative variables, while the Kruskal-Wallis test was applied for comparing groups with non-normally distributed quantitative variables. Fisher's Least Significant Difference (LSD) was used as a post-hoc test to determine the group that created the difference. Multiple logistic regression analysis was conducted to investigate the risk factors for iron deficiency anemia. Results were deemed statistically significant if they reached a confidence level of 95% with a significance level of < 0.05 .

RESULTS

The review of records identified a total of 493 children eligible for enrolment. After excluding children as per the criteria, a final sample consisted 196 boys out of 371 children with mean (SD) aged 9 (1) months were enrolled (**Fig. 1**). The mean (SD) duration of iron consumption was 5 (2) months. A total of 174 (46.9%) children used liposomal iron, 137 (36.9%) used ferric, and 60 (16.2%) used ferrous iron for prophylaxis.

Table I presents the descriptive data of the children. Among 371 infants, 35 (9.5%) had iron deficiency anemia and 143 (38.5%) had iron deficiency. 193 (52.0%) infants had normal iron parameters.

Table II provides a comparison of participant characteristics and blood parameters based on the type of iron prophylaxis utilized. The age and gender distribution was similar ($P > 0.05$). Infants who received ferrous iron had lowest rate of iron deficiency anemia with similar rate between ferric iron and liposomal iron use; $P = 0.019$ on analyzing iron deficiency and iron deficiency anemia in relation to weight, height percentiles, and feeding practices of the infants did not yield any statistically significant differences ($P > 0.05$). A significant difference was noted between the groups for both values ($P = 0.001$ and $P = 0.008$). Fisher's Least Significant Difference (LSD) was used as a post hoc test to determine the group that created the difference, and it was revealed that only the ferrous group showed significant differences in terms of anemia and ferritin levels compared to the other groups ($P < 0.05$).

Table III shows the outcomes of univariate logistic regression of risk factors for iron deficiency wherein ferrous and liposomal iron preparations seemed to offer significant benefit in reducing risk for iron deficiency. In the multivariate analysis, the risk of developing iron deficiency was significantly lesser with use of ferrous formulation [OR (95% CI) 0.04 (0.01 - 0.15, $P < 0.001$)] but not with liposomal iron [1.26 (0.80-1.97; $P = 0.319$).

DISCUSSION

This study compared the efficacy of diverse iron preparations (ferrous, ferric, and liposomal) for iron prophylaxis in healthy infants. A higher prevalence of iron deficiency and iron deficiency anemia among

children receiving prophylaxis with liposomal and ferric iron preparations in contrast to those on ferrous iron was reported.

The WHO highlights the prevalence of anemia in children aged 6 to 59 months as 40% worldwide [14]. In our study, focusing on infants regularly using iron supplementation, 38.5% exhibited iron deficiency, while 9.5% experienced iron deficiency anemia. It's essential to recognize that our research, conducted in tertiary care hospitals, reflects the specific patient demographic within that context. Yalçın et al in their nationwide study reported a 7.3% overall prevalence of anemia, with 68.8% of children receiving preventive ferrous iron supplementation [15]. Another study illustrated that 30.3% of infants faced iron deficiency, with 20.2% progressing to iron deficiency anemia. Notably, around 63% of their participants regularly utilized ferric iron prophylaxis [16]. The present study reported iron deficiency and iron deficiency anemia in a significant proportion of children on iron prophylaxis, similar to the forementioned studies that used ferrous or ferric iron prophylaxis [15,16]. These findings emphasize the urgent need to evaluate the effectiveness of various infant iron preparations.

A comprehensive review of studies on prevention of micronutrient deficiencies in children under five years of age in low- and middle-income countries (LMICs) identified effective strategies like use of iron alone, iron-folic acid supplementation, multiple micronutrient supplementation, micronutrient powders, targeted fortification, and large-scale fortification [17]. Organizations, both from high-income countries and LMICs, recommend routine screening of infants for iron deficiency anemia at 9-12 months of age [18,19].

In the present study, infants receiving ferrous iron demonstrated higher hemoglobin values compared to other groups, as reported earlier [20]. A meta-analysis of eight studies, emphasized the superiority of ferrous iron over iron polymaltose complex in increasing hemoglobin and ferritin levels for treating iron deficiency anemia in children [21]. In recent years, the benefits of liposomal iron in patients with gastrointestinal issues and intolerance to standard iron treatments have been evaluated [22]. Infants on liposomal iron had a higher risk of iron deficiency than the ferrous iron group in this study. A few studies suggest similar efficacy and safety of liposomal iron as intravenous iron in treating anemia in chronic kidney disease [23], and chemotherapy-related anemia [10]. Another study on children with iron deficiency (aged 3 months to 12 years) found lower hemoglobin levels in liposomal iron recipients at two weeks compared to ferrous gluconate/sulfate [24]. The present study found no significant differences in weight and height percentile based on iron deficiency or anemia. However proportion of children categorized for weight and height were different as per iron prophylaxis methods. Most of the infants who consumed ferrous iron had weight and height, within the 10th to 90th percentiles suggesting a positive impact on growth. Anemic infants had lower weight-for-age z-scores in an earlier study, suggesting factors beyond iron deficiency that can affect growth [15]. The impact of iron on final length and weight remains uncertain.

The majority of infants were exclusively breastfed for the initial 6 months in this study. However, no significant association was detected between feeding patterns and iron deficiency or anemia. A separate study highlighted a higher prevalence of anemia among infants breastfed for less than 6 months, emphasizing the importance of iron supplementation not only during pregnancy but also initiating oral iron at 4-6 months' age

for infants [25]. Our results emphasize the need for enhanced counseling, breastfeeding support, and professional training to combat anemia.

The present study had a few limitations. The retrospective approach limited access to data on iron content of children's diets, and ensuring compliance, potentially confounding the results. The results were based on data from two hospitals, which might limit generalizability. To ensure robustness, future studies should involve diverse populations and settings. Another limitation was unequal group distribution as the number of infants utilizing ferrous formulation was smaller compared to the other two groups. It is essential to conduct more extensive prospective studies to address these limitations and obtain a more comprehensive understanding of factors that determine iron intake, side effects associated with iron supplementation, and relevant outcomes.

The result of this study unequivocally supports ferrous iron's safety for infant prophylaxis. Given the crucial role of iron in the initial two years of growth, it is vital to start iron prophylaxis. Future studies should explore the efficacy and safety of iron formulations in infants on traditional iron supplements. Rigorous trials are essential for a better understanding of efficacy and safety of liposomal in this patient group.

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WHAT THIS STUDY ADDS?

- Iron deficiency anemia was seen in a small proportion of infants on iron prophylaxis.
- Ferrous iron was superior to liposomal iron or ferric iron in preventing iron deficiency.

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Table I Descriptive Data of Enrolled Children (n = 371)

<i>Variables</i>	<i>Value</i>
<i>Feeding</i>	
Breastfeeding	264 (71.2)
Breast feeding+ Formula	87 (23.5)
Formula	20 (5.4)
<i>Weight percentile</i>	
< 3 percentile	6 (1.6)
3-10 percentile	14 (3.8)
10-90 percentile	321 (86.5)
90-97 percentile	24 (6.5)
>97 percentile	6 (1.6)
<i>Height percentile n(%)</i>	
< 3 percentile	6 (1.6)
3-10 percentile	12 (3.2)
10-90 percentile	327 (88.2)
90-97 percentile	22 (5.9)
>97 percentile	4 (1.1)
<i>Labotary findings^a</i>	
Hb (mg/dL)	12.0 (1.1)
Ferritin (µg/L)	18.7 (13.8)
Hemocrit (%)	36.1 (2.9)
RDW (%)	13.9 (2.5)
MCV (fL)	76 (6.0)
<i>Prophylactic Iron Supplementation</i>	
Ferric	137 (36.9)
Ferrous	60 (16.2)
Lipozomal iron	174 (46.9)
<i>Iron status</i>	
Iron deficiency	143 (38.5)
Iron deficiency anemia	35 (9.5)

Data is presented as n(%) and ^amean (SD).

Hb Hemoglobin, MCV Mean corpuscular volume, RDW Red blood cell distribution width

Table II Comparison of Clinical and Laboratory Profile Based on Iron Supplementation

	<i>Iron Supplementation</i> (<i>n</i> =371)			<i>P values</i>
	Fe ⁺³ (<i>n</i> =137)	Fe ⁺² (<i>n</i> =60)	Liposomal iron (<i>n</i> =174)	
Age ^a (mo)	9.1 (1.3)	9.4 (1.3)	9.2 (1.3)	0.079
Gender				
Female	56 (40.9)	30 (50.0)	89 (51.1)	0.178
Male	81 (59.1)	30 (50.0)	85 (48.9)	
Feeding				
Breastfeeding	82 (59.9)	48 (80.0)	134 (77.0)	0.006 ^b
Breast feeding+ Formula	45 (32.8)	11 (18.3)	31 (17.8)	
Formula	10 (7.3)	1 (1.7)	9 (5.2)	
Weight percentile				
<3 percentile	1 (0.7)	-	5 (2.9)	0.037 ^b
3-10 percentile	7 (5.1)	-	7 (4.0)	
10-90 percentile	120 (87.6)	58 (96.7)	143 (82.1)	
90-97 percentile	8 (5.8)	2 (3.3)	14 (8.0)	
> 97 percentile	1 (0.7)	-	5 (2.9)	
Height percentile				
<3 percentile	1 (0.7)	-	5 (2.9)	0.022 ^b
3-10 percentile	4 (0.7)	-	8 (4.6)	
10-90 percentile	124 (90.5)	58 (96.6)	145 (83.2)	
90-97 percentile	7 (5.1)	2 (3.3)	13 (7.5)	
> 97 percentile	1 (0.7)	-	3 (1.7)	
Ferritin status				
<12 µg/L (<i>n</i> =178)	75 (48.9)	3 (3.3)	100 (54.6)	< 0.001 ^b
≥12 µg/L (<i>n</i> =193)	62 (51.1)	57 (96.7)	74 (45.4)	
Anemia				
Hb <11 mg/dL (<i>n</i> = 35)	14 (10.2)	-	21 (12.1)	0.019 ^b
Hb ≥11 mg/dL (<i>n</i> = 336)	123 (89.8)	60 (100)	153 (87.9)	
Iron status				
Iron deficiency anemia (<i>n</i> = 35)	14(10.2)	-	21 (12.1)	< 0.001 ^b
Iron deficiency (<i>n</i> = 143)	61(44.5)	3 (5.0)	79 (46.0)	
Normal (<i>n</i> = 193)	62 (45.3)	57 (95.0)	74 (41.9)	
Serum ferritin (ng/mL) ^a	17.6 (14.5)	30.1 (10.8)	15.4 (12.1)	< 0.001
Hemoglobin (g/dL) ^a	11.9 (1.1)	12.4 (0.8)	12.0 (1.1)	0.008
Mean corpuscular volume (fL) ^a	75.9 (5.5)	77.2 (4.5)	75.7 (5.9)	0.184
Red Cell distribution width ^a	13.9 (2.2)	13.3 (2.1)	13.8 (2.8)	0.227

Data expressed as *n* (%) or ^amean (SD)

^bSignificantly different for ferrous group compared to ferric and liposomal iron groups

Table III Factors Influencing Iron Deficiency in the Blood

<i>Factor</i>	<i>Univariate Logistic Regression Analysis</i>		
	OR (95% CI)	β	<i>P</i> value
Iron preparation for prophylaxis			
Ferric	0.74 (0.48-1.13)	-0.30	0.164
Ferrous	0.03 (0.01-0.13)	-3.45	< 0.001
Liposomal iron	0.45 (0.30-0.68)	-0.80	0.001
Age	0.96 (0.81-1.12)	-0.05	0.570
Gender	1.44 (0.96-2.19)	0.37	0.081
Feeding status in the first six mo	1.5 (0.96-2.36)	0.41	0.076
Weight between 10-90 percentile	1.1 (0.35-3.58)	0.11	0.857
Height between 10-90 percentile	0.79 (0.22-2.77)	0.24	0.709

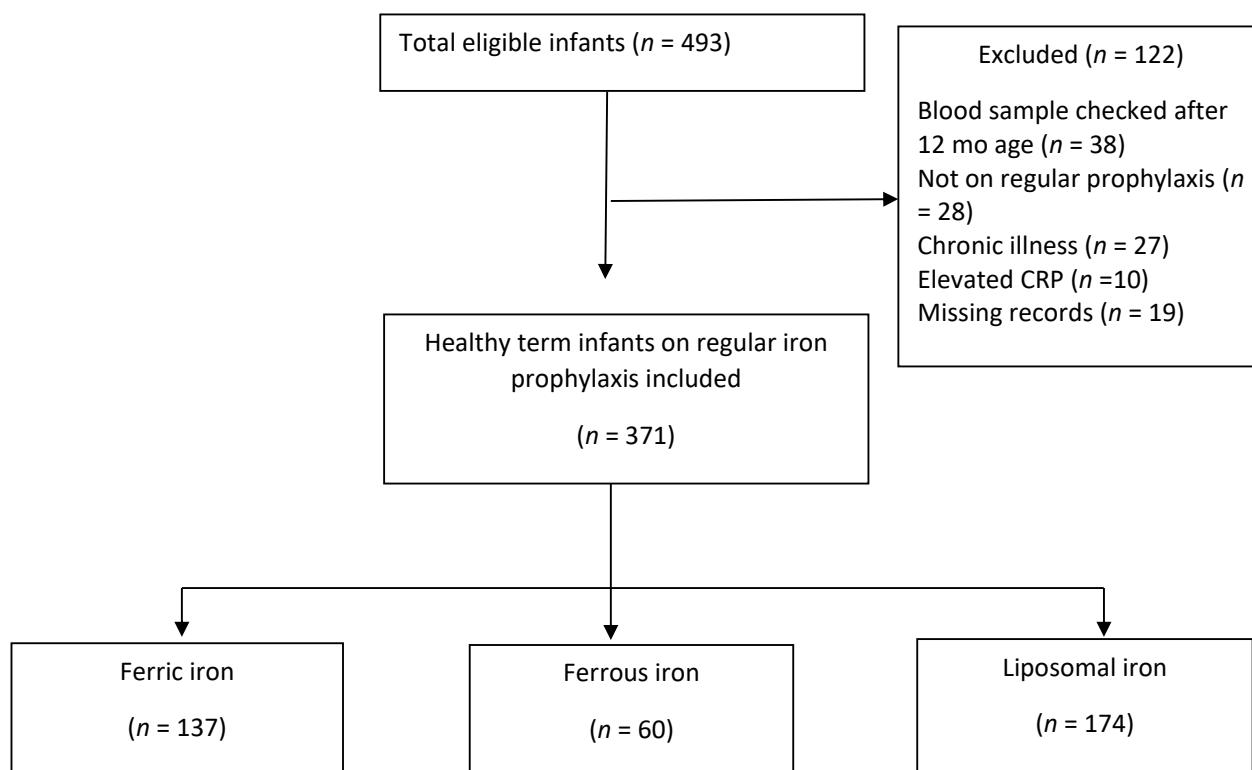


Fig. 1 Enrolment of study participants