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ORJINAL RESEARCH
ORJİNAL ARAŞTIRMA

Anne Sütü Alan İnfantlarda Demir Takviyesinin Etkisi: Randomize Kontrollü Çalışma

Effect Of Iron Supplementation In Breastfed Infants: A Randomized Controlled Study

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ABSTRACT

Aim

The purpose of this study was to investigate the efficacy of daily iron supplementation for prevention of iron-deficiency and iron-deficiency anemia in healthy exclusively breast-fed infants and the factors affecting development of iron-deficiency anemia.

Methods

This study was conducted with 65 infants (35 in the iron supplemented group and 30 in the non-supplemented controls) between January 2009-March 2010. Detailed physical examination of all infants was carried out at ages 4, 6, and 9 months. Iron-rich complementary feeding recommendations were given to all families when their infants were 6 months and 9 months of age. Anthropometric measurements, Denver developmental screening test, complete blood count and iron parameters were evaluated.

Results

There were no significant differences in terms of having iron-deficiency or iron-deficiency anemia between infants receiving iron supplementation and control group not receiving iron supplementation (31.44% 46.6%, respectively) (p>0,05). There were also no statistically significant differences between supplemented and non-supplemented groups in terms of anthropometric measurements, hematological parameters, Denver developmental screening results.

Conclusion

Consumption of iron rich complementary foods together with routine iron supplementation of term, breast-fed infants from 4 months of age can improve their iron status. Receiving sufficient iron in diet is an effective way prevent iron-deficiency anemia.

Keywords: breastfed infant, diet, iron, iron deficiency, iron deficiency anaemia

ÖZET

Amaç

Bu çalışmanın amacı, çoğunlukla anne sütü alan infantlarda demir eksikliği ve demir eksikliği anemisinden korunmada günlük oral demir takviyesinin etkisini ve demir eksikliği gelişimini etkileyen faktörleri incelemektir.

Metod

Bu çalışma Ocak 2009-Mart 2010 tarihleri arasında, 65 infant (35 demir desteği alan ve 30 destek almayan kontrol grubu) ile yürütülmüştür. Tüm infantlara 4, 6 ve 9. aylarında detaylı fizik muayene yapıldı. Demirden zengin beslenme önerileri infantlar 6 ve 9. ayında iken tüm ailelere verildi. Antropometrik ölçümler, Denver gelişimsel tarama testi, tam kan sayımı ve demir parametreleri değerlendirildi.

Sonuçlar

Demir desteği alan ve kontrol grubu infantlar arasında demir eksikliği ve demir eksikliği anemisi gelişimi yönünden belirgin fark yoktu (31.44%, 46.6% sırasıyla) (p>0,05). Gruplar arasında aynı zamanda, antropometrik ölçümler, hematolojik parametreler, Denver gelişimsel tarama testi sonuçları arasında belirgin fark izlenmedi.

Tartışma

Term, anne sütü alan infantlarda, 4 aylıktan itibaren verilen rutin demir takviyesi ile birlikte demirden zengin ek besinlerin tüketimi demir durumunu düzeltebilir. Diyetle yeterli demir alımı demir eksikliği anemisinden korumada etkin bir yoldur.

Anahtar kelimeler: anne sütüyle beslenen bebek, diyet, demir, demir eksikliği, demir eksikliği anemisi

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INTRODUCTION

Iron-deficiency anemia (IDA) and iron deficiency (ID) without anemia is the most prevalent micronutrient deficiency in the world (1). IDA and ID during infancy and childhood produce long-lasting detrimental effects on growth, neurodevelopment and cognitive functions (2- 5). The healthy term infants usually have sufficient neonatal iron stores until 4 to 6 months of age (6). These stores have been reduced by 4 months of age, and exogenous iron is required to prevention of developing IDA. Strategies for prevention of ID and IDA in infants inlude, food-based approaches, i.e. dietary improvement or iron fortified complementary foods, iron supplementation, and maternal education (3,7). World Health Organization (WHO) recommends iron supplementation to all children between 6 and 23 months of age where diet does not include iron fortified foods, or prevalence of anemia in children at 1 year of age is high (above 40%) (3). Also American Academy of Pediatrics recommends that exclusively breastfed or partially breastfed infants receive an iron supplementation of 1 mg/kg per day, starting at 4 months of age and continue until appropriate complementary foods are introduced (1). However, there are also concerns about the early universal iron supplementation of breastfeeding infants (8).

The purpose of this study was to investigate the efficacy of daily iron supplementation for prevention of ID and IDA in healthy exclusively breast-fed infants and the factors affecting development of IDA.

MATERIALS AND METHODS

This prospective randomized controlled trial was conducted among infants attending the General Pediatrics and Social Pediatrics outpatient clinics of Dr. Sami Ulus Training and Research Hospital. The approval of the ethics committee of the aforementioned hospital was obtained. This study was carried out between January 2009 and March 2010. Families of infants who were eligible for the inclusion to the study were informed about the study and written informed consent was taken from all families. Only infants who met following criteria were considered eligible: (1) Gestational age more than 37 weeks and birth-weight more than 2500 g, (2) singleton birth, (3) no known genetic diseases and major congenital malformation, (4) uneventful perinatal history, (5) no chronic disease, (6) no known hematologic disorder of mother-infant dyads, (7) no history of iron supplementation or therapy, (8) no history of blood transfusion, (9) mothers intended to breast-feed exclusively until 6 months of age, to continue breastfeeding with introduction of complementary foods no earlier than 6 months of age.

Venous blood samples (5ml) were obtained from 90 infants who met the inclusion criteria and whose families accepted to participate in the study to assess their hemoglobin (Hb), hematocrit (Htc), mean corpuscular volume (MCV), red cell distribution width (RDW), serum iron, serum iron binding capacity (SIBC), transferrin saturation (TS) and ferritin. ID was defined as a ferritin level lower than 10 µg/L, and IDA was defined Hb<10.3 gr/dl (9, 10). Eight infants with ID or IDA on admission were given iron treatment and excluded from the study. Remaining 82 infants were recruited into two groups by simple randomization, the first group receiving iron supplementation (n=42) and the second group no iron supplementation (n=40). The iron supplement was a commercially available formulation of ferrous sulfate containing 30 mg/ml of elemental iron.

The supplement was given at dose corresponding to 1 mg of elemental iron per kg per day. Mothers of the infants in the supplementation group were cautioned to give the iron supplement 1 h before or two hours after feedings other than breast milk. The iron dose was adjusted monthly according to the infant's weight. In this study, an infant was defined as exclusively breastfed when he or she received only human milk without any other fluid or food. Between 4 and 6 months, the infants were excluded when mother gave any foods or fluids. Complementary feeding recommendations were given to all families by the same pediatrician when their infants were 6 months of age.

Detailed physical examination of all infants including anthropometric measurements (weight, height, head circumference) was carried out at ages 4, 6, and 9 months. Compliance with the study protocol in terms of iron supplementation, side effects, breastfeeding, and complementary feeding was based on mother's daily checklist and followed by monthly house calls.

When the infants reached 9 months of age, venous blood samples were taken for Hb, Htc, MCV and RDW, serum iron, SIBC, and ferritin levels and their parents were asked to fill a standard 24 hour diet form for the infants to calculate the dietary iron content. Diet lists were evaluated with the Nutrition Information System (BeBis) Program (Epispro for Windows, Stuttgart, Germany: Turkish version BeBis, Version 4, Data bases) for that age. Recommended dietary allowance (RDA) for iron was determined 11 mg at this age group (1). Iron supplements were not included in the calculation.

Complete blood counts (Hb, Htc, MCV and RDW) were determined using a daily calibrated ABX Pentra 80 device and electrical impedance method. Serum iron and SIBC were measured by Coulter Beckman Lx20 device and spectrophotometric methods, and serum ferritin was determined by an Immunolite Bio DPC device, using the chemiluminescence immunoassay method. TS was calculated by dividing serum iron by SIBC.

Data were analyzed by using the SPSS for Windows 16.0 program. Shapiro Wilk test, Student's t-test, Mann–Whitney U test, Pearson correlation test, Chi-square test and Forward stepwise logistic regression (binary logistic regression) test was used for analysis of various variables. Statistical significance was defined as $p<0.05$.

RESULTS

During the enrollment period, parents of 1078 infants aged 4 months were invited to the study. Of these, 560 infants had exclusion criteria. Initially, the parents of 90 infants gave consent for the study. After initial complete blood count analysis, 8 infants with ID or IDA were given iron treatment and excluded from the study. On follow-up, families of 3 infants did not want to use iron supplementation and left the project. Eight infants were dropped out and 6 infants were excluded due to early introduction of supplementary foods. The study was completed with a total of 65 infants (35 in the iron supplemented group and 30 in the non-supplemented controls) (Fig 1). The total dropout rate was not significantly different between two groups.

There was no difference between two groups in terms of gender, birth-weight, gestational age, initial mean weight, height, head circumference, number of maternal gravida and parity and monthly income levels of families (Table 1).

On admission at age 4 months, no significant differences were found among the two groups (receiving iron supplementation and those who did not) in terms of the initial Hb, Htc concentrations, RDW, MCV, serum iron

Table 1: Initial characteristics of infants in the two groups.

	Supplemented group (n=35)	Control Group (non-supplemented) (n=30)	Statistics
Gender (male/female)	22/13	17/13	X^2=0.26, p=0.61
Mean birth weight (gr)	3238±395.2	3271.6±433.0	p=0.75
Mean gestational age (week)	39.4±1.2	39.17±1.3	p=0.50
Mean weight (initial)	6400±287	6450±235	p=0.35
Mean height (initial)	62.1±3.4	62.4±3.7	p=0.40
Mean head circumference (initial)	40.3±1.5	40.5±1.4	p= 0.45
Maternal gravida 1/≥2	17/18	15/15	X^2=0.01 p=0.91
Maternal parity 1/≥2	21/14	15/15	X^2=0.65 p=0.42
Monthly income (TL)<1000/>1000	22/13	23/7	X^2=1.45 p=0.23

transferrin saturation, and serum ferritin levels. Also there was no difference between two groups in terms of mean Hb, Hct, MCV, RDW, ferritin levels at age 9 months except for mean transferrin saturation levels (Table 2). Mean TS levels of non-supplemented control group were significantly lower compared with of supplemented group (p=0.03) Mean ferritin levels of non-supplemented group was lower than those of supplemented group at age 9 months but this difference was not found statistically significant (Table 2).

Table 2: Comparison of hematologic parameters between supplemented and control groups at the 4th and 9th months (Student's t-test for independent samples)

Time	Hematologic parameters	Supplemented group (n=35)	Control Group (non-supplemented) (n=30)	t	p
4th month	Hemoglobin	11.4±0.6	11.7±0.8	1.331	0,19
	Hematocrit	33.3±2.3	33.8±2.5	0.688	0,49
	MCV*	76.3±4.7	77.8±4.0	1.088	0,28
	RDW†	11.6±0.6	11.4±0.9	0.549	0,59
	Ferritin	87.1±82.6	94.7±84.2	0.301	0,77
	Transferrin Saturation	13.1±6.2	15.7±8.5	1.087	0,28
9thmonth	Hemoglobin	11.4±0.8	10.9±0.9	1.813	0,08
	Hematocrit	33.9±2.1	32.7±2.5	1.653	0,11
	MCV	73.5±6.5	72.5±5.25	0.614	0,54
	RDW	13.7±1.4	13.5±1.5	0.423	0,68
	Ferritin	43.3±46.0	24.3±20	1.876	0,67
	Transferrin Saturation	17.6±10.6	9.9±5.1	3.209	0,03

* MCV: Mean corpuscular volume (MCV),

†: Red cell distribution width (RDW).

Eleven (31, 4%) of 35 infants receiving iron supplementation had ID or IDA, whereas 14 (46, 6%) of 30 infants in control group not receiving iron supplementation had ID or IDA at the age of 9 month-old. This difference was not statistically significant ($\chi2=1.585$, $p=0.208$) (Table 3). Five of 35 infants in supplemented group and 12 of 30 infants in control group had IDA and this difference was statistically significant ($\chi2=5.53$, $p=0.019$) (Table 3).

Mean iron intake in the diet at 9 months was 5.7±3.2 mg in supplemented and 6.03±3.53 mg in non-supplemented group. In terms of mean amount of dietary iron no difference was found between iron supplemented and non-supplemented control groups, (Student's t test for independent samples, $t=0.46$, $p=0.65$).

Table 3: Comparison of ID and IDA rates of iron supplemented and non-supplemented control groups Chi-square test)

	Supplemented group (n=35)	Control Group (non-supplemented) (n=30)	Total (n=65)	Statistics
IDA	5 (14. 2%)	12 (40%)	17 (26.2)	χ^2=5.53, p=0.019
ID	6 (17. 2%)	2 (6.7 %)	8 (12.3%)	
ID or IDA (total)	11 (31.4)	14 (46. 7%)	25 (38.5%)	X^2=1.585 p=0.208

There were no statistically significant differences between supplemented and non-supplemented groups in terms of weight gain, height and head circumferences at the 6th and 9th month follow up (p>0.05) (Table 4).

The infection rates of study and control groups were not statistically significantly different (Chi-square test, χ2=0.03, p=0.87).

Table 4: Comparison of growth parameters of study and control groups (Student's t-test for independent samples)

	Supplemented group (n=35)	Control Group (non-supplemented) (n=30)	t	P
Mean weight 4 mo (kg)	6400±287	6450±235	0.947	0.35
Mean height 4 mo (cm)	62.1±3.4	62.4±3.7	0.848	0.40
Mean head circumference 4 mo (cm)	40.3±1.5	40.5±1.4	0.764	0.45
Mean weight 6 mo (kg)	7380±1040	7420±970	0.367	0.715
Mean height 6 mo (cm)	64.9±3.1	65.3±4.1	0.212	0.832
Mean head circumference 6 mo (cm)	42.7±1.5	42.9±1.5	1.282	0.204
Mean weight 9 mo (kg)	8.990±1320	9260±1170	0.865	0.390
Mean height 9 mo (kg)	72,4±4,2	72.8±3.8	0.382	0.704
Mean head circumference 9 mo (cm)	45.3±1.8	45.7±2.3	0.614	0.541

In our study, ID or IDA developed in 25 infants (38, 4%) overall. We made an analysis of factors affecting development of IDA and found that mothers' education level, maternal gestational anemia, and usage of iron supplementation and gravida of mothers were not significantly important factors (p>0.05) (Table 5). Using forward stepwise logistic regression analysis, we determined that iron supplementation decreased the risk of IDA by a factor of 3.34 (OR=0.299, p=0.041) (Table 5).

While the diet of 20 (30.7%) infants of total 65 patients included sufficient iron for their age (11mg and more), 45 (69.3%) infants did not receive sufficient iron in their diet. While only 2 of 20 infants receiving 11 mg or more iron in diet developed IDA, 23 of 45 infants obtaining insufficient iron in diet had IDA. Forward stepwise logistic regression analysis showed that receiving sufficient iron in diet prevented development of IDA (OR=0.769, p=0.003) (Table 5).

Table 5 Analysis of the possible independent factors influencing development of IDA (Forward stepwise logistic regression).

Variables	ID or IDA* (-) (n=40)	ID or IDA (+) (n=25)	P
Gravida ± SD	1.96 ± 1.35	2 ± 0.94	0.72
Mother's Education(n=65) Illiterate Primary School High School University	 3 23 14 8	 1 13 3 0	 0.27
Anemia during pregnancy (+) (n=23) Anemia during pregnancy (-) (n=42)	17 31	6 11	 0.86
Iron supplementation during pregnancy (+) (n=44) Iron supplementation during pregnancy (-) (n=21)	32 16	12 5	 0.72
Monthly income <1000TL (n=45) >1000TL (n=20)	 35 13	 10 7	 0.72
Sufficient dietary iron intake (n=20) Non-sufficient dietary iron intake (n=45)	18 22	2 23	 0.003
Iron supplementation (n=35) Control group (n=30)	24 16	11 14	 0.041

* IDA: Iron deficiency anemia.

DISCUSSION

In our randomized controlled study, at 9 months of age iron supplemented infants' hematologic parameters were slightly higher than those of non-supplemented group and these differences were not statistically significant except for mean TS levels. One possible explanation is that limited numbers of infants were enrolled in the study.

However, when we compared ID and IDA numbers of supplemented and non-supplemented groups, our study results demonstrated that iron supplementation reduced the development of IDA (Table 3) and also using forward stepwise logistic regression analysis we determined that iron supplementation decreased the risk of ID or IDA (Table 5).

To date several studies have been conducted evaluating the efficacy of iron supplementation on the prevention of IDA (10-14). In a study, iron supplementation significantly decreased iron deficiency anemia in Honduran infants, but a similar effect was not observed among Swedish infants. In this study, it was also reported that iron supplementation at age 4 months was not superior to supplementation started at 6 months of age (11). Authors of this study concluded that iron supplementation of term, breast-fed infants from 4 to 6 months to at least 9 months of age can improve iron status and reduce anemia in socioeconomically disadvantaged populations where IDA is prevalent.

In another study, which had a limited number of cases, 3 months of daily or weekly iron supplementation was not found to decrease the likelihood of IDA (14). The authors also concluded that proper nutritional supplements in the diet had a positive effect on iron stores of infants, independent of iron supplementation. In a recent study, although iron supplementation wasn't found effective on the prevention of IDA, mean ferritin levels were significantly high in the iron-supplemented group, and there was a significant positive correlation between iron intake by food and Hb value at 12 months of age (10). In our study, 31, 4 % ID or IDA prevalence despite iron prophylaxis in the supplemented group indicates that there must be multiple factors playing role in development of IDA. Maternal iron level, birth weight, gestational age and umbilical cord clamping time are factors that largely determine body iron content in the first 6 months of life (15). Using forward stepwise logistic regression analysis, we found that mothers' education level, gestational anemia, usage of iron supplementation in pregnancy and gravida of mothers were not significantly important factors for development of IDA. As it was reported in the recent study by Gokcay et al. (10), in this study, it was showed that receiving sufficient iron in diet prevented development of IDA (Tablo 5). However, there are differences between our study and this study in terms of study design and starting time of complementary feeding.

In our study, infection rates of study and control groups were not significantly different. Other studies gave conflicting results concerning iron supplementation and infection rate. Studies have shown beneficial effect (16), no effect (17), and an increase in infectious illnesses (18, 19). Systematic review of 28 randomized controlled trials on 7892 children demonstrated that iron supplementation has no apparent harmful effect on the overall incidence of infectious illnesses in children, though it slightly increases the risk of developing diarrhea (20).

In our study, for supplemented and non-supplemented groups there were no statistically significant differences for weight gain, height and head circumferences at the 6th and 9th month follow- up. The evidence from well-designed intervention trials evaluating the effect of iron supplementation on physical growth in children is conflicting. Some studies have shown significant improvement in physical growth with iron supplementation (21) while other investigators found no such benefit (22). Another interesting dimension has been added by the possibility of a detrimental effect of iron supplementation on physical growth in iron-replete children (23).

Our study had some limitations. No placebo was used and we noted that the parents of the non-supplemented group may have paid special attention to the diet of their infants in terms of iron-containing foods.

As a conclusion, recommendation of iron rich complementary foods and iron supplementation of term, breast-fed infants from 4 months of age can improve their iron status and reduce anemia especially in socioeconomically disadvantaged populations where IDA is prevalent.

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