Is there enough evidence for intermittent iron supplementation?

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Abstract

The high prevalence of Iron Deficiency Anemia (IDA) in later infancy has been correlated to the progressive depletion of iron stores and predominantly cereal based diet consumed in developing countries. Both daily and weekly iron supplementations have been documented to improve hematological status in children; however there is a paucity of similar data in the age group of 6 to 24 months, particularly in non anemic infants. The present study was therefore designed to generate the relevant information in this context. This prospective randomized controlled trial enrolled babies in two groups, one receiving daily iron and the second group received weekly iron. Anthropometric and hematological parameters were recorded at baseline and at the end of 3 months. . The daily group had a significantly greater increase in hemoglobin at 3 months as compared to the weekly group (p value = 0.000). The daily group had a significantly greater increase in serum Ferritin at 3 months as compared to the weekly group (p value = 0.000). we conclude that daily iron supplementation is more efficacious than weekly iron supplementation in non anemic term babies in the age group of 6 to 24 months.

Keywords: *Iron Deficiency Anemia (IDA), Daily Iron supplementation, Weekly iron Supplementation, Hemoglobin (Hb), Serum Ferritin*

1. Introduction

Iron deficiency anemia (IDA) is the most prevalent nutritional deficiency worldwide and the adverse effects of IDA on the critical rapid growth and development period of infancy are well known (Lozoff et al, 2006). It is estimated that globally 1.62 billion people suffer from anemia, and IDA is responsible for about half of those cases (Benoist et al, 2008). As the relatively high hemoglobin concentration of the newborn infant falls during the first 2-3 months of life, considerable iron is reclaimed and stored. These reclaimed stores usually are sufficient for

blood formation in the first 6-9 months of life in term infants (Norma et al, 2010). Iron deficiency usually starts manifesting around the age of six months. The development of iron deficiency at this age is correlated to the fact that the infant stores become depleted by this time and demand increases. Prematurity, breast feeding for less than six months duration, use of non-iron fortified formula, introduction of cow's milk before 1 year of age and diet deficient in iron predispose to iron deficiency anemia (Oski,1993). By 4 months of age, neonatal iron stores have been reduced by half and exogenous iron is required to meet the needs of normal growth and development. The American Academy of Pediatrics (AAP) recommends that daily iron supplementation should be initiated at the age of 4 months in term infants (Baker and Greer, 2010). The World Health Organization (WHO) has recommended that intermittent iron supplementation is an effective alternative of daily iron supplementation in preschool age group (WHO, 2011).

Daily iron supplementation beginning in later infancy in predominantly breast fed term infants has been documented to increase hemoglobin by 0.7 g/dl after 2 months of iron supplementation (Nagpal et al, 2004). However, daily iron supplementation results in higher incidence of gastrointestinal side effects leading to poor compliance (Sharma & Mahajan, 2014). During infancy, daily iron supplementation is recommended, but some clinical trials have shown that intermittent iron supplementation (e.g., weekly, every third day) is as efficacious as daily supplementation in terms of improving iron status (Thu et al, 1999 and Arcanjo at al, 2013). Weekly iron supplementation is well studied in adolescents and older age groups (Pena-Rosas et al, 2012).

Therefore, iron supplementation on a weekly instead of a daily basis may increase the compliance due to lesser side effects; is cost effective and may increase the efficiency of iron supplementation during infancy. To date, the efficacy of weekly iron supplementation has not been investigated fully in healthy, term, exclusively breast-fed infants. In addition, studies on routine iron supplementation of exclusively breast-fed infants are also limited.

The focus of action, formerly placed on treatment, is moved to the prevention of IDA. However, daily administration was more efficacious (by about 5-10%) than the weekly regimen in most scenarios considered (Gross et al, 2005 and Smuts et al, 2005). The results of four subsequent studies, adopting the International Research on Infant Supplementation Initiative (IRIS) protocol, in which daily and weekly supplementation were compared among infants, indicate that only daily supplementation is efficacious in controlling anemia (De Romana et al, 2005).

The purpose of this study is to determine the efficacy of daily and weekly iron supplementation for 100days to improve the iron status of 6 to 24 months old healthy babies without iron deficiency (ID) or IDA.

There is paucity of literature in this age group of 6 to 24 months. Therefore in countries like India where the prevalence and severity of iron deficiency is high, further evaluation of these two supplementation strategies is needed.

2. Material & Methods

The study was conducted in Vardhman Mahavir Medical College and the Department of Pediatrics, Safdarjung Hospital, New Delhi, India after approval by the Institutional Ethics Committee/Institutional Review Board. The study was an Open label non blinded Randomised Controlled Study. The study was carried over a period of 1.5 years between October 2012 to April 2014. This was carried out in the outpatient department of Department of Pediatrics, Safdarjung Hospital.

2.1 Inclusion and exclusion criteria
Inclusion criteria

- Apparently Healthy 6 to 24 months old babies
- Birth weight >2500g
- Born by full term singleton pregnancy
- Predominantly breastfed in the first 6 months of life

Exclusion criteria

- Hemoglobin<11g%
- Major congenital abnormality
- Any adverse event requiring hospitalization
- H/O chronic disease or perinatal disease
- Previous history of blood transfusion or blood sampling >10ml
- H/O iron supplementation/therapy
- Anemic mother
    - Malnutrition
    - H/O bleeding disorder

2.2 Outcome Variables
   Primary outcome variables
   ➢ Infant hemoglobin
   ➢ Serum ferritin
   ➢ Peripheral smear for type of anemia
   (All these three parameters were evaluated at the time of enrolment and at the end of 3 months. About 2 ml of blood sample was drawn each time).
   Secondary outcome variables

Infant growth parameters (anthropometry)

   ➢ Weight
   ➢ Length
   ➢ Head circumference
      (All these parameters were evaluated at the time of enrollment, end of 1st month, 2nd month, 3rd month)

2.3 Sample size= 100

The primary outcome variable for sample size consideration was infant's hemoglobin. On the basis of data from an earlier study it was estimated that 40 babies will be required in each group. With 90% power and 5% significance level, to detect a difference in hemoglobin value of at least 30% between the two groups, sample size came out to be 50 in each group assuming 20% attrition (loss to follow up)

2.4 Randomization

6 to 24 months old babies were randomly divided into 2 equal groups on the basis of random numbers generated by computer sequences

> Group1: daily iron supplementation (1mg elemental iron/kg/day)
> Group 2: weekly iron supplementation (2mg elemental iron/kg/week)

Doses were adjusted monthly according to the weight. Liquid suspension of iron (ferrous sulphate) and folic acid which were commercially available in the hospital free of cost were provided, it contained 100mg of elemental iron and 0.5mg folic acid in 5ml.

Iron deficiency anemia was defined as:

HEMOGLOBIN< 11g/dl
S. FERRITIN< 12 µg/L

2.6 Follow Up- follow up was done monthly for 3 months

2.7 Investigations-
  ➢ Hemoglobin of the mother at recruitment
    Infant:
  ➢ Primary

Assessment	At 0 month	After end of 3 months
Hemoglobin		
Serum ferritin		
Peripheral smear for type of anemia		

  ➢ Secondary

Assessment	At 0 month	After end of 3 months
Head Circumference		
Weight		
Length		

Hemoglobin estimation was done using automated hematology analyzer sysmex XT-2000i; and sysmex KX-21 which uses the principle of fluorescent flow cytometry, using the direct current detection method with coincidence correction. S.ferritin was measured with the help of

immunoradiometric tests. The weight was measured using lever scale to the nearest 100g. Head Circumference was measured using a non-stretchable measuring tape with least count of 1mm. The length was measured with the help of infantometer to the nearest 1mm.

2.8 Data Analysis

Data was analysed using SPSS for Windows (SPSS Inc.,Chicago,IL). Differences among the two groups i.e. Statistical significance of quantitative variables was determined by unpaired student t-test and non parametric mann whitney test. The frequencies of Iron Deficiency Anemia among the 2 groups i.e. Statistical significance of qualitative variables was determined by chi-square test and fischer exact test. p value ≤ 0.05 was taken as level of statistical significance

3. Results

3.1 Baseline Characteristics of study population
A total of 125 babies fulfilled the recruitment criteria and were enrolled for the prospective follow up (Group 1- daily iron supplementation, Group 2- weekly iron supplementation). 103 of recruited babies reported for follow up after 100 days.

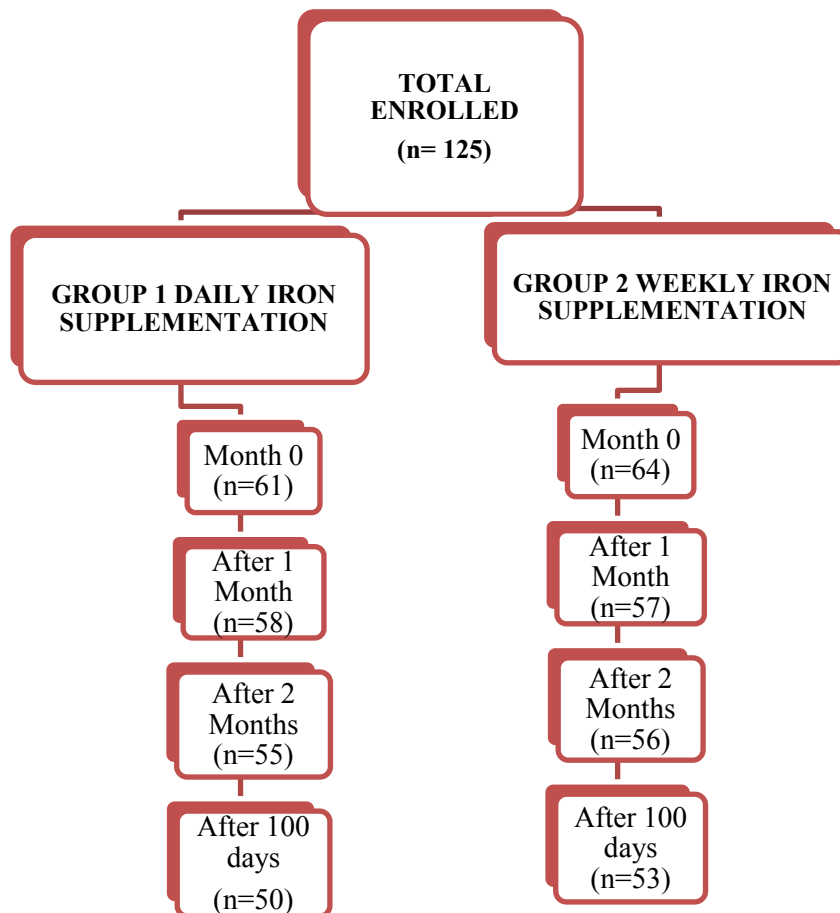Figure-1: Enrolment, Randomization, Participation And Follow Up Of Babies In The Study

Figure-1 shows that 125 babies fulfilled the inclusion criteria and were enrolled for this study. Of the 125 babies randomized; 61 babies were allotted in the daily iron supplementation group and 64 babies were allotted in the weekly iron supplementation group. In the daily group; 58 babies reported for follow up at the end of first month, 55 babies reported for follow up at the end of two months and 50 babies reported for follow up at the end of 3 months. Similarly in the weekly group; 57 babies reported for follow up at the end of first month, 56 babies reported at the end of two months and 53 babies reported for follow up at the end of 3 months. An analysis was done to determine whether the babies who have not reported for follow up had comparable baseline characteristics with those reporting for follow up. The two groups were statistically comparable for various baby and maternal characteristics. No significant difference was found between the two groups.

The relevant baseline characteristics of all the babies who completed the trial were analyzed. They babies were comparable in all the characteristics.

Table-1: Comparison of Baseline Characteristics of Babies between the two groups

CHARACTERISTIC	DAILY IRON GROUP (n= 50)	WEEKLY IRON GROUP (n=53)	p VALUE
Age (months)	14.26 ± 7.001	13.11 ± 5.679	0.184

Sex:
    Male (%)
    Female (%)
	
	29 (58)
	21 (42)
		
		35 (66)
		18 (34)
			
			0.401

Birth weight (kg)	2.808 ± 0.2237	2.742 ± 0.1769	0.101
Current morbidity	0 (0)	0 (0)	-
Weight at recruitment (kg)	9.210 ± 1.5488	9.132 ± 1.4779	0.794
Length at recruitment (cms)	75.52 ± 7.6944	74.142 ± 6.3248	0.322
Head Circumference at recruitment (cms)	44.82 ± 1.7779	44.792 ± 1.5110	0.933
Hemoglobin (gm/dl)	11.49 ± 0.796	11.42 ± 0.454	0.576
Serum Ferritin (ng/ml)	56.404 ± 34.4221	52.649 ± 26.1854	0.533

NCNC- Normocytic Normochromic; NCHC- Normocytic Hypochromic; MCHC- Microcytic Hypochromic

3.2 Outcome measures

3.2.1 Hematological parameters in response to iron supplementation

The babies in the two groups were studied for their hematological response to supplementation at the end of 3 months. The hematological parameters included hemoglobin (Hb), peripheral smear and serum Ferritin. As seen in Table-2 below, there is significantly greater increase in Hb as well as Ferritin stores with daily iron supplementation at the need of 3 months. At the end of 3 months, all the babies in both

the groups had normocytic normochromic peripheral smear. There was no statistical difference between the two groups.

Table-2: Comparison of Hemoglobin (In gm/dl) and Serum Ferritin (ng/ml) At 0 & at end of 3 months

Time Period	Group 1: Daily Group (n=50) Mean ± Standard Deviation (SD)	Group 2: Weekly Group (n=53) Mean ± Standard Deviation (SD)	p Value
Hb At Recruitment	11.49 ± 0.796	11.42 ± 0.454	0.576
Hb At end of 3 months	11.882 ± 0.3237	11.683 ± 0.4264	0.009
S. Ferritin At Recruitment (ng/ml)	56.404 ± 34.4221	52.649 ± 26.1854	0.533
S. Ferritin At end of 3 months (ng/ml)	101.704 ± 23.0263	62.149 ± 24.2079	0.000

3.2.2 Anthropometric parameters in response to supplementation

Both daily as well as weekly iron supplementation had no effect on weight, length/height and head circumference.

4. Discussion

This study was done to evaluate the efficacy of daily iron supplementation versus weekly iron supplementation in non anemic children in the age group of 6 to 24 months.One hundred and three (103) babies out of the 125 enrolled babies completed the study. As seen in Figure-1, 11(18%) babies in the daily group and 11 (17.2%) babies in the weekly group were lost to follow up at the end of 3 months. The reasons for this rate of loss of follow up were

- Reporting from a distance to the hospital for follow up and no reimbursement for transportation and loss of wages (7 babies in daily group and 4 in weekly group)
- Lack of perceived benefit of medication in apparently healthy children (3 babies in daily group and 7 babies in weekly group)
- Blood sampling at 0 and end of 3 months (1 baby in daily group)
- Prolonged duration of medication for no apparent disease (1 baby in weekly group)

The baseline characteristics in both the daily and weekly iron supplementation group were comparable. The daily group had a higher increase in hemoglobin and serum Ferritin as compared to the weekly group (p value = 0.000). Both daily and weekly groups had normocytic normochromic picture on the peripheral blood smear at the end of 3 months. No statistically significant difference was observed in the secondary outcome variables namely weight, length/height and head circumference after 3 months of supplementation in both the groups.

Various studies have compared daily iron supplementation with weekly iron biweekly iron supplementation. In a study by Azeredo et al which compared the efficacy of daily versus weekly iron supplementation in 103 non anemic children aged between 6 to 18 months, it was seen that daily supplementation was more efficacious and there was no statistical difference in the side effects and adherence in both the groups. However, the loss to follow up was 25% in daily group and 21.6% in weekly group. The limitation of this study was that it did not measure the serum ferritin (indicator of iron stores in the body), there was no control group and the sample size was small. In another study conducted in Brazil by Engstrom et al included babies aged between 6 to 12 months, daily iron supplementation alone was found to be effective in increasing hemoglobin and decreasing risk of anemia compared to weekly iron supplementation. Limitation of the study was the use of only hemoglobin concentration as the outcome variable. Serum ferritin levels were not measured in this study. Also hemoglobin concentrations were not measured at the baseline and hence the change in hemoglobin at the end of intervention was not available. De Romana et al found that daily iron supplementation was more effective than weekly mutimicronutrient supplementation in preventing fall in serum ferritin levels in a study conducted in Peru. This study included 313 anemic babies in the age group of 6-12 months which were randomly assigned to 4 treatment arms, a daily placebo arm, a daily group that received 10 mg of iron as ferrous fumarate, a daily multiple micronutrient group or a weekly dose of multiple micronutrients. Another study conducted in Kenya by Desai et al concluded that daily iron supplementation was better than biweekly iron supplementation. However unlike in our study; the babies in this study were in the age group of 2 months to 5 years, the babies were mild to moderately anemic and the region in which this study was conducted was endemic for malaria.

All the above mentioned studies have corroborated the findings of our study; that daily iron supplementation is superior to intermittent iron supplementation. However there are some studies which have concluded that both daily and intermittent iron supplementation are equi-efficacious. Arcanjo et al found that both weekly and daily iron supplementation were effective in increasing hemoglobin levels and reducing anemia in infants. This study had 176 babies in the age group of 12 to 24 months; the babies were anemic (mean Hemoglobin 9.7gm/dl in the daily group and 8.8 gm/dl in the weekly group at baseline). The limitation was of this study was that serum ferritin was not measured in the babies for the assessment of iron stores. Another study by Khademloo et al that was conducted in Iran concluded that weekly iron supplementation was equally effective in increasing hemoglobin levels as compared to the daily supplementation. This study enrolled 100 non anemic babies in the age group of 6-24 months. However an increase in serum ferritin levels was seen only with the daily iron supplementation and not with the weekly group. Thu et al also found that the increase in hemoglobin was comparable in both the daily and weekly group. Their study was conducted in 168 6-24 months old Vietnamese children; 47% children were anemic; vitamin A and zinc supplementation was also given in both the groups. The findings of our study on growth parameters (weight, length) were also confirmed by this study. A study in Jordan evaluated the effectiveness of daily supplementation versus biweekly versus weekly supplementation and concluded that weekly and biweekly iron was as effective as daily iron supplementation (Faqih et al, 2006). However the babies in this

study were anemic and in the age group of 2-6 years; only 63 of the 124 recruited children completed the study; measurements of final serum ferritin concentration were available for only 12, 12, and 10 children in daily (n=45), weekly (n=45), and biweekly (n=44) groups respectively.

There were some studies which showed that daily and intermittent iron supplementations were comparable in increasing the hematological parameters; but claimed intermittent was better due to its better tolerability. A study in China by Liu et al in 238 anemic children (6yrs old) found that weekly and biweekly doses were as effective as the daily dose in controlling anemia, had insignificant side effects (7% children in biweekly and 4% in weekly group experienced side effects in contrast to 36% of those receiving the daily dose). It also concluded that the twice weekly dose had no advantages over the weekly dose.

Some studies have compared the efficacy of biweekly and daily supplementation. Schultink et al concluded that biweekly iron supplementation has an effect similar to that of daily iron supplementation in preschool, anemic Indonesian children. Another study in India by Awasthi et al compared daily and biweekly iron supplementation; a total of 400 and 403 children in the age group of 3 to 6 years were enrolled in daily and biweekly regimes, respectively, of which 57.32 per cent and 50.25 per cent were anemic (Hb <11 g/dl) in each group. Adherence in biweekly and daily regimes was 89.05 per cent vs. 63.5 per cent. This study concluded that biweekly as well as daily administration is effective in raising hemoglobin levels and decreasing community prevalence of anemia significantly. However, since there is better adherence and lower drug costs associated with biweekly iron administration, this can be considered for programme use.

5. Policy Implications

The National Iron Plus Initiative 2013 in India has recommended bi-weekly 20 mg elemental iron and 100 microgram (mcg) folic acid (per ml of liquid formulation) for 100 doses in a year and age appropriate biannual de-worming, with dose half tablet of albendazole between 1-2 years age and full tablet from the age of 2 years onwards for preschool children of 6-59 months. These guidelines have replaced the National Nutritional Anemia Control Programme which recommended daily iron supplementation with iron and folic acid for 100 days in babies aged 1 to 5 years.

However as discussed in our study, there have been very few studies which have found the biweekly iron supplementation to be superior to daily and weekly approaches. The scientific evidence that exists favours the daily supplementation approach to a greater extent as compared to the intermittent iron supplementation. The findings of our study have also added to the pool of scientific evidence that exists in favour of the daily approach.

Hence there is a need to conduct further studies to compare the different treatment approaches on a wider scale.

6. Conclusions

Both daily and weekly iron supplementation led to significant improvements in haematological parameters (Hb, Serum Ferritin and Peripheral smear) of non anemic babies in 6 to 24 months age group, who were started on complementary feeds. Daily iron supplementation schedule was superior in efficacy in terms of benefit in Hb concentration and serum ferritin values.The prevalence of anemia was 0 % in both daily and weekly groups at the end of 100 day study period. Daily iron supplementation was found to be more effective in preventing depletion of iron (Ferritin) stores compared to weekly supplementation schedule. More studies are needed to be carried out on a larger sample size for a longer period of time with a better follow up rates to validate this observation. Both daily and weekly iron supplementation did not result in any significant difference in growth parameters of babies compared during the 100 days of study period.

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