Weekly versus Daily Iron Supplementation for Preventing Iron deficiency Anaemia Amongst Children Between Six to 24 Months: A Randomised Control Trial

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ABSTRACT

Introduction: Iron deficiency anaemia is common in developing nations and starting iron supplementation from infancy is an important measure for its prevention. There is still not enough evidence, whether giving iron twice weekly as compared to daily, is enough to prevent the same.

Methods: This open-labeled randomised control trial was conducted at a tertiary care facility over a period of 1.5 years. After informed consent from parents, a total of 125 non-anaemic healthy infants in age group six to 24 months; with birth weight > 2500 grams, born singleton at term gestation and predominantly breastfed in the first six months of life; were randomised using computer generated sequence to two groups. Control group received daily elemental iron supplementation of 1 mg/kg/day and the intervention group received twice weekly 2 mg/kg/day. Haemoglobin, serum ferritin were measured at enrolment and at the end of 100 days. Primary outcome was anaemia defined as haemoglobin less than 11 mg/dl. Secondary outcome measures were weight gain, increase in length and occipito-frontal circumference.

Results: Baseline characteristics were similar in the two groups. This study showed significantly higher mean haemoglobin (mg/dl) (mean ± SD 11.882 ± 0.3237, 11.683 ± 0.4264, p = 0.009) and mean serum ferritin (ng/ml) (mean ± SD 101.704 ± 23.0263, 62.149 ± 24.2079, p = 0.000) at end of 100 days in the control group than the intervention group. There was no difference in any of the secondary outcomes.

Conclusions: Biweekly iron supplementation can also prevent iron deficiency anaemia in children between six to 24 months of age but daily is better in respect to the increase in haemoglobin.

Key words: anaemia; anaemia prevention; iron deficiency; iron supplementation; serum ferritin
INTRODUCTION

Iron deficiency anaemia (IDA) is the most prevalent nutritional deficiency worldwide which affects growth and development. The global prevalence of anaemia among the pre-school children is 47.4%. Haemoglobin concentration of the newborn infant falls during the first two to three months of life, considerable iron is reclaimed and stored are sufficient for blood formation in the first six to nine months of life in term infants. Iron deficiency usually starts manifesting around the age of six months. By four months of age, neonatal iron stores get reduced by half and exogenous iron is required to meet the needs of normal growth and development. The American Academy of Paediatrics (AAP) recommends that daily iron supplementation should be initiated at the age of four months in term infants. The World Health Organisation (WHO) has recommended that intermittent iron supplementation is an effective alternative to daily iron supplementation in preschool age group.

Daily iron supplementation beginning in late infancy in predominantly breast fed term infants has been documented to increase haemoglobin by 0.7 g/dl after two months of iron supplementation. However, daily iron supplementation results in higher incidence of gastrointestinal side effects leading to poor compliance.

During infancy, daily iron supplementation is recommended, but some clinical trials have shown that intermittent iron supplementation (e.g., biweekly, every third day) is as efficacious as daily supplementation in terms of improving iron status. Decreasing frequency to biweekly may increase the compliance due to lesser side effects; is cost effective and may increase the efficiency of iron supplementation during infancy. However, daily administration was more efficacious (by about 5-10%) than the weekly regimen in most scenarios considered. The focus of action which was formerly placed on treatment has now moved on to the prevention of IDA. To date, the efficacy of biweekly iron supplementation has not been investigated fully in healthy, term, exclusively breast-fed infants. In addition, studies on routine iron supplementation among exclusively breast-fed infants are also limited. So, the purpose of this study is to determine the efficacy of daily and weekly iron supplementation for 100 days to improve the iron status of six to 24 months old healthy babies without anaemia.

METHODS

This open labeled randomised study was carried out over a period of 1.5 years at a tertiary care teaching hospital in the outpatient department of Paediatrics. The trial was registered with central trials registry of India CTRI: REF/2018/02/017594. The institutional ethics committee approved the study. Subject were healthy infants in the age group six to 24 months with birth weight > 2500 grams, born singleton at term gestation and predominantly breastfed in the first six months of life. Those with anaemia defined as haemoglobin less than 11 gm/dl, congenital malformation, already on iron supplements and those who received blood transfusion were excluded. Other parameters like demographic, maternal factors were also recorded. Subjects were randomised using computer generated sequence to two groups and 1:1 allocation ratio after taking informed consent from the parents or guardians. Sample size was calculated as 50 in each group with power 90% to detect 30% difference in haemoglobin between the two groups, 5% significance, 10% attrition rate on follow up at three months. A total of 125 children were recruited. 61 children were randomised to control group to receive daily elemental iron (liquid preparation containing 100 mg elemental ferrous sulphate plus folic acid 0.5 mg per 5 ml available from hospital supply) supplementation at 1 mg/kg/day and 68 to intervention group to receive weekly at 2 mg/kg/day.

Primary outcome was anaemia defined as haemoglobin less than 11 gm/dl. Secondary outcome measures were weight, length and occipito-frontal circumference (OFC). Haemoglobin, serum ferritin, peripheral smear for type of anaemia and anthropometry were taken at baseline and after three months of iron supplementation. Babies were followed monthly for three months.
Haemoglobin was analysed using cyanide free method automated analyser (Sysmex XT-2000i and KX-21 which uses fluorescent flow cytometry principle using the direct current detection method with coincidence correction). Serum ferritin was measured by using immune-radiometric assay (Beckman Coulter Access-2). Weight was measured using lever scale to the nearest 100 g. OFC was measured using a non-stretchable measuring tape with least count of one mm. The length was measured with the help of infantometer to the nearest one mm. Data was analysed using SPSS for Windows (SPSS Inc.,Chicago, IL). P value less than 0.05 was taken as significant.

RESULTS
A total of 125 babies fulfilled the recruitment criteria & were enrolled for the prospective follow up. At the end of three months, 51 babies in control group and 53 in intervention group could be followed up. (Figure 1).

Baseline characteristics were similar in the two groups. (Table 1) Daily supplementation group had significantly higher mean haemoglobin (gm/dl) (mean ± SD 11.882 ± 0.3237, 11.683 ± 0.4264, p = 0.009) and mean serum ferritin (ng/ml) (mean ± SD 101.704 ± 23.0263, 62.149 ± 24.2079, p < 0.001) as compared to biweekly group after three months of supplementation.

The means of the percentage increase in haemoglobin and serum ferritin showed similar results (p < 0.05) when compared in different subgroups male:female and six to 12 and 12 to 24 months age group babies. Both daily and weekly groups had normocytic normochromic picture on the peripheral blood smear after 100 days of supplementation. No significant difference was observed in any of the secondary outcome variables weight, length and head circumference after three months of supplementation in both the groups (Table 2).

DISCUSSION
The objective of the study was to evaluate the efficacy of daily versus weekly iron supplementation in non-anaemic children in the age group of six to 24 months. Both the groups were comparable considering the basal characteristics, which indicates good randomisation. The possible reasons for the loss of follow up (17.6%) could be reporting from a distance and loss of wages, lack of perceived benefit of medication in apparently healthy children, prolonged duration of medication for no apparent disease and poor educational and socioeconomic status.

The age group of six to 24 months was selected as high prevalence of iron deficiency anaemia is seen in this age group due to the progressive depletion of iron stores, inadequate dietary intake of iron and the low bioavailability of iron in the complementary feeds introduced after six months of age.14-17

This study showed that after 100 days of iron supplementation, the daily group had a significantly higher haemoglobin, haemoglobin increase in percentage and serum ferritin as compared to the weekly group. The increase in serum ferritin was not found by some researchers in healthy non-anaemic breast fed infants.21

Various studies have compared daily with biweekly iron supplementation. Azeredo et al. studied 103 non-anaemic children aged between six to 18

Figure 1. Study Flow Chart
months and Engstrom et al six to 12 months and showed daily supplementation was more efficacious without difference in side effects and adherence in both the groups. They used only haemoglobin concentration as the outcome variable and serum ferritin levels were not measured. A study in Kenya by Desai et al. concluded that daily iron supplementation was better than biweekly iron supplementation. However, the study population was between two months to five years, mild to moderately anaemic and the region 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. Few studies, in the similar age groups by Arcanjo et al. and Hademloo et al. have concluded that both weekly and daily iron supplementation were effective in increasing haemoglobin levels and reducing anaemia in infants but an increase in serum ferritin levels was seen only with daily iron supplementation.

Some studies have compared the efficacy of biweekly and daily supplementation in anaemic children in different age groups like in Indonesia by Schultink et al. and Thu et al. (had cases similar to our age group) and found similar results but better adherence in biweekly group. Tavil et al.
found biweekly regime to be superior with higher haemoglobin and serum ferritin levels, lesser side effects and being cost effective, as compared to daily regime in 94 anaemic Turkish children in the age group of five months to six years. All these studies showed equal benefits in both types of supplementation in anaemic children and not the normal healthy children. Systematic review in Cochrane database by De-Regil et al. concluded that intermittent iron supplementation was as effective as daily iron supplement in improving haemoglobin (MD -0.60 g/L, 95% CI -1.54 to 0.35, 19 studies) and ferritin concentrations (MD -4.19 µg/L, 95% CI -9.42 to 1.05, 10 studies) and advocated intermittent iron supplementation for public health interventions in settings where daily supplementation has failed or has not been implemented.

In the latest meta-analysis by Tom E et al. in 2020, subgroup analyses by frequency of supplementation showed a significant difference in risk of anaemia among daily versus weekly iron-folic acid regimens, with weekly regimens showing greater benefit (p for subgroup differences = 0.01), though only one study contributed data to the latter group. We did not find any difference in anthropometric measurements between the two study groups after three months of supplementation and these findings were similar to Smuts et al.

Pasrichia et al. conducted systematic review and meta-analysis, included included 45 studies with 42000 children aged four to 23 months of age with daily iron supplementation and found children randomised to iron had slightly lesser length (SMD -0.83, -1.53 to -0.12; eight studies, n = 868) and weight gain (-1.12, -1.19 to -0.33). They felt the need of adequately powered studies to address the uncertain adverse effect profile and effect on growth with daily iron supplements.

Though meta-analyses and systematic review by Low M et al amongst school age children found daily iron supplementation to improve age-adjusted height among all children and age-adjusted weight among anaemic children; adherence was good but safety concerns remained. We studied healthy breast fed children and found increase in both serum ferritin and haemoglobin by iron supplementation which is also a clear recommendation stated by review of systematic reviews for iron supplementation. Considering increase in both the haemoglobin and serum ferritin, which is a marker of iron storage, it is prudent to supplement iron daily to prevent anaemia in cases of increased requirement or loss from the body as in poor nutrition and warm infestation, both of which are very common in developing countries.

There are some limitations to the study. Firstly, the compliance to treatment in both groups could only be assessed telephonically and relied on the parents verbal statements at the time of assessment points. Secondly, we did not study the cognitive outcomes or the side effect profile of iron supplementation in both groups, which is a concern raised by few studies.

### CONCLUSIONS

Biweekly iron supplementation can also prevent iron deficiency anaemia in healthy non-anaemic children between six to 24 months of age, but daily supplementation is better with respect to increase in haemoglobin.
REFERENCES


