Daily Versus Weekly Iron and Folic Acid Supplementation Regimen- A Randomized Parallel Open Label Trial among Reproductive Age Group Women in an Urban Poor Locality of Bengaluru

Vairavasolai P¹, Jayanthi Srikanth², Madhusudan M³

¹Assistant Professor, Department of Community Medicine, Madurai Medical College, Madurai, Tamil Nadu, India

²Professor, Department of Community Medicine, Kempegowda Institute of Medical Sciences, Bengaluru, Karnataka, India

³Associate Professor, Department of Community Medicine, DM Wayanad Institute of Medical Sciences, Wayanad District, Kerala, India

Correspondence: Dr Madhusudan M., **Email:** madhusudan_kims12@rediffmail.com

Abstract:

Introduction: The global prevalence of anaemia in non-pregnant women is 30.2% and in India it is 53.2%. At least half the burden of anaemia is associated with iron deficiency. Women of reproductive age are at higher risk of developing iron deficiency because of losses during menstruation. Though Daily supplementation with iron and folic acid for a period of 3 months has been the standard as an approach for the prevention and treatment of iron deficiency anaemia among women of reproductive age, there has been limited success with the daily regimen in public health programmes. Intermittent use of oral iron supplements has been proposed as an effective alternative. **Objectives:** To compare the effectiveness of weekly and daily oral iron and folic acid therapy in improving the Hemoglobin levels among the reproductive age group women, adverse effects and compliance to both the regimens. **Method:** This was a comparative Randomized parallel open label trial conducted in an urban poor locality of Bengaluru conducted between January 2014 and January 2016. All the women in the reproductive age group (15-45 years) with mild to moderate anemia were included in the study. Sample size of 106 subjects was randomly allocated into the 2 groups (53 into weekly regimen and 53 into daily regimen). The subjects were supplemented with IFA tablets for 3 months according to their regimen. **Results:** Mean increase in Haemoglobin (Hb) in the daily group (1.92 ± 1.1 g/dl) was significantly ($p < 0.01$) more when compared to that in the weekly group (0.91 ± 0.82 g/dl). Incidence of all the Adverse Drug Reactions (ADRs) were more in the daily group compared to weekly group. However, the difference was only significant for abdominal pain and metallic taste ($p < 0.01$ and 0.02 respectively). The proportion of subjects reporting at least one ADR was also significantly more ($p < 0.01$) in the daily group compared to the weekly group. Compliance for weekly regimen (97.12%) was found to be significantly better ($p < 0.01$) when compared to that of the daily regimen (94.07%). **Conclusions:** Daily regimen was more effective in raising the hemoglobin levels when compared to weekly regimen. Incidence of abdominal pain and metallic taste were significantly more in the daily group compared to weekly group. Compliance for weekly regimen was significantly better when compared to that of the daily regimen.

Key words: Iron and Folic acid supplementation, Reproductive age group women, Iron Deficiency Anemia, Hemoglobin

Introduction:

It is estimated that the global prevalence of anaemia in non-pregnant women is 30.2% and in India it is 53.2%.^[1,2] Anaemia has multiple causes that very

often coexist; it can result from parasitic infections, inflammatory disorders, inherited disorders of haemoglobin structure, or vitamin and mineral deficiencies, including iron and vitamins A, B12 and

Access this article online:

Quick Response Code

Website:

www.healthlinejournal.org

DOI:

10.51957/Healthline_153_2020

How to cite this article: Vairavasolai P, Srikanth J, Madhusudan M. Daily Versus Weekly Iron and Folic Acid Supplementation Regimen- A Randomized Parallel Open Label Trial among Reproductive Age Group Women in an Urban Poor Locality of Bengaluru. Healthline.2020;11(2):21-27.

folate. At least half the burden of anaemia is associated with iron deficiency. Iron deficiency is the result of prolonged negative iron balance, which can be caused by inadequate iron intake (due to insufficient dietary iron content or absorption), increased iron requirements or chronic loss of iron due to bleeding. Women of reproductive age are at higher risk of developing iron deficiency because of losses during menstruation.^[3]

Iron deficiency anaemia impairs resistance to infection in all age groups, and reduces physical capacity and work performance among adolescents and adults.^[3,4] In addition, women entering pregnancy with suboptimal iron reserves may be at higher risk of negative maternal and neonatal outcomes.^[5] Daily supplementation with iron and folic acid for a period of 3 months has been the standard approach for the prevention and treatment of iron deficiency anaemia among women of reproductive age. Despite its proven efficacy, there has been limited success with the daily regimen public health programmes, which is thought to be primarily due to low coverage rates, insufficient tablet distribution and, and low adherence because of the side-effects (e.g. constipation, dark stools or metallic taste).^[6]

Intermittent use of oral iron supplements (i.e. once, twice or three times a week on non-consecutive days) has been proposed as an effective alternative to daily iron supplementation to prevent anaemia among menstruating women.^[7,8] The proposed rationale behind this intervention is that intestinal cells turn over every 5–6 days and have limited iron absorptive capacity. Thus intermittent provision of iron would expose only the new epithelial cells to this nutrient, which should, in theory, improve the efficiency of absorption.^[9,10] Intermittent supplementation may also reduce oxidative stress and the frequency of other side-effects associated with daily iron supplementation as well as minimize blockage of absorption of other minerals due to the high iron levels in the gut lumen and in the intestinal epithelium.^[5,7] Experience has shown that intermittent regimens may also be more acceptable to women and increase compliance with supplementation programmes.^[11,12] Use of these regimens may also result in improvement in women's iron and folate status prior to pregnancy, to help prevent neural tube

defects.^[13] Government of India has implemented weekly oral iron folic acid supplementation (WIFS) programme to bring down the high prevalence of anemia among adolescents and thereby break the intergenerational cycle of anemia. Under the programme supervised weekly iron and folic acid supplements of 100mg elemental iron and 500µg folic acid will be administered to adolescents using a fixed day approach.^[14]

There are no studies done among reproductive age group women in this part of the country to assess the effectiveness of weekly versus daily oral iron supplementation to improve the iron status of the women. Hence, in this context the present study was done to compare the effectiveness of weekly and daily oral iron and folic acid therapy in improving the Hemoglobin levels among the reproductive age group women, adverse effects and compliance to both the regimens.

Method:

This was a comparative Randomized parallel open label trial conducted in Yarab Nagar, an urban poor locality under the urban field practice area of Kempegowda Institute of Medical Sciences (KIMS), Bengaluru between January 2014 and January 2016. Institutional Ethics Committee (IEC) approval was obtained prior to the start of the study. All the women in the reproductive age group (15-45 years) with mild to moderate anemia and those willing to participate were included in the study. Mild anemia was defined as pallor of conjunctiva and/or mucous membranes, moderate as pallor of skin in addition to criteria for mild anemia and severe as pallor of palmar creases in addition to criteria for moderate anemia.^[15] Women who were pregnant, lactating, those with any known hemoglobinopathies, chronic disease of liver, Cardio Vascular System (CVS), kidney and those currently taking or having taken therapeutic iron in the previous 6 months were excluded from the study. Sample size was calculated using the formula

$$n = \frac{z^2pq}{d^2}$$

$z = 1.96$ (Z value corresponding to a confidence level of 95%)

p (prevalence of anemia among reproductive age group women from previous studies)=56% i.e., 0.56¹⁶
 $q=1-p=44\%$ i.e., 0.44

$d(\text{margin of error})=10\% \text{ i.e., } 0.1$

Substituting these values in the formula, a sample size of 96 was arrived at.

Study was conducted in 2 phases. In the first phase, a house-to-house survey was conducted covering a population of 12,385 in 2987 houses to identify all the women in the reproductive age group which came to 2209. All these women were clinically screened for anemia and 322 were found to be anemic. All these 322 women were line listed and they formed the sampling frame. Using simple random sampling technique, 106 subjects (96 + an additional 10% to compensate for dropouts if any) were selected randomly from this sampling frame after applying the inclusion and exclusion criteria. The details regarding socio demographic characteristics were collected using predesigned and pretested standardized questionnaire. All the 106 subjects were line listed and randomly allocated into the 2 groups (53 into weekly regimen and 53 into daily regimen) by using coin tossing method.

Informed written consent was taken from all the subjects for the intervention study. Initial deworming was done by giving Tablet albendazole 400 mg single dose for both the groups. Baseline Hemoglobin reading was done using Hemocue Hb 301 system for both groups. The HemoCue system utilizes the principle of oxidation of haemoglobin to hemiglobin by sodium nitrite and the subsequent conversion of hemiglobin to hemiglobinazide by sodium azide. The reagents for these reactions are contained within a small disposable microcuvette of approximately 10 microliters in volume. A venous or capillary sample is introduced into the microcuvette by capillary action and, after reaction with the reagents, the absorbance is read in the HemoCue photometer at 565 and 880 nm. The haemoglobin concentration is then displayed as a digital reading, in either g/dl or mmol/l in 15-45 seconds.^[17]

The subjects were visited every Monday for 3 months and given IFA tablets (containing 100mg elemental iron and 0.5 mg folic acid) for entire week. Those in the daily group were given 7 tablets (at the rate of 1/day) of which the first tablet was consumed under the supervision of the investigators. The consumption of remaining 6 tablets was ensured by checking the empty blister packs in the subsequent

visit. Those in the weekly group were given 1 tablet/week which was consumed under the supervision of the investigators. Constant motivation was given to all the subjects to consume tablets as per the schedule during every visit. Hemoglobin estimation was done after completion of 3 months of therapy. The number of tablets consumed and number not consumed in each group were noted. Compliance to each regimen was assessed based on the proportion of the number of tablets consumed out of the number to be consumed.

The Data were entered in Microsoft excel and analyzed using SPSS-21 version. Descriptive statistics such as percentages, mean, standard deviation and Inferential statistics like Paired 't' test (to find out significance of the mean increase in hemoglobin value before and after the therapy), Unpaired 't' test (to find out the significance of difference between mean increase in hemoglobin between weekly and daily IFA group) and χ^2 test (to find out the significance of difference between proportions of adverse reactions and compliance in weekly and daily group) were used.

Results:

There were 13 drop outs (5 in weekly and 8 in daily group) and finally 93 subjects (weekly =48, daily=45) were followed up for 3 months. The mean age of the subjects in the weekly group and daily group were 33.9 ± 7.1 years and 35.0 ± 8.0 years respectively. Around 26(54.2%) and 21(46.7%) of the subjects were Muslims in the weekly and the daily group respectively and 22(45.8%) and 24(53.3%) Hindus. Forty-four (91.7%) and 41(91.1%) were married in the weekly and daily groups respectively and 4(8.3%) and 4(8.9%) unmarried. 15(31.3%) and 12(26.7%) were from the lower middle class in the weekly and daily groups respectively, 33(68.7%) and 31(68.9%) from upper lower, 0(0%) and 2(4.4%) from lower class as per the modified Kuppuswamy's classification.

The prevalence of consumption frequency of more than or equal to once a week of green leafy vegetables and fruits were more among weekly regimen group and that of non-vegetarian food, legumes and nuts were more among daily regimen group. However these differences were not found to be significant by Chi square test ($p=0.93, 0.96, 0.75, 0.11$ and >0.99 respectively)[Table 1].

It was noted that in both the groups there was

Table 1: Comparison of consumption of iron rich foods between weekly and daily regimens

Food item		Frequency of Consumption		Total	p value
		< once a week	> once a week		
GLV	Weekly regimen	3(6.25)	45(93.75)	48(100)	0.93*
	Daily Regimen	4(8.89)	41(91.11)	45(100)	
Non vegetarian food	Weekly regimen	12(25)	36(75)	48(100)	0.75
	Daily Regimen	10(22.22)	35(77.78)	45(100)	
Legumes	Weekly regimen	10(20.83)	38(79.17)	48(100)	0.11
	Daily Regimen	4(8.89)	41(91.11)	45(100)	
Fruits	Weekly regimen	35(72.92)	13(27.08)	48(100)	0.96
	Daily Regimen	33(73.33)	12(26.67)	45(100)	
Nuts	Weekly regimen	46(95.83)	2(4.17)	48(100)	>0.99*
	Daily Regimen	43(95.56)	2(4.44)	45(100)	

*Fischer's exact test was used as the cells had expected counts <5

Table 2: Comparison of mean Hb% before & after intervention in weekly and daily groups

Group	Mean Hb before intervention (gm/dl)	Mean Hb after intervention (gm/dl)	t value*	95% C. I.		p value
				Lower	Upper	
Weekly group	10.10±1.25	11.02±1.31	-7.675	-1.57	-0.67	<0.01
(n=48)						
Daily group	9.76±1.35	11.68±1.46	-11.229	-2.26	-1.15	<0.01
(n=45)						

*Paired 't' test with 2-sided C.I .95% was used

Table 3: Comparison of mean rise in Hb between weekly & daily groups

Hemoglobin	Weekly group	Daily group	t value*	95% C. I.		p value
	(n= 48)	(n=45)		Lower	Upper	
Mean increase in Hb (gm/dl)	0.91±0.82	1.92±1.1	-4.896	-1.42	-0.59	<0.01

*Two sample independent 't' test with 2-sided C.I .95%

increase in mean Hb levels after the intervention and both these increases were found to be statistically highly significant by Paired 't' test ($p=0.001$ for each) [Table 2].

It was noted that mean increase in Hb in the daily group was more when compared to that in the weekly

group and this difference was also found to be statistically highly significant by unpaired 't' test ($p<0.01$) [Table 3].

Abdominal pain was the most common ADR in the daily group and abdominal pain and nausea were the most common ADRs in the weekly group. Incidence of

Table 4: Comparison of adverse effects of Iron & folic acid tablets in the daily and weekly groups

Adverse Drug Reaction	Weekly group(n=48)	Daily group(n=45)	p value
Abdominal pain	4(8.3)	23(51.1)	<0.01
Nausea	4(8.3)	5(11.1)	0.92*
Metallic taste	2(4.1)	9(20.0)	0.02
Diarrhea	0(0)	1(2.2)	0.97*
At least one ADR	10(20.8)	32(71.1)	<0.01

Figures in parenthesis indicate percentages. The total exceeds 100% as multiple responses were present.

*Yate's correction was used as expected cell count was < 5.

Table 5: Comparison of compliance to weekly and daily regimens

Regimen	No. Consumed (%)	No. not consumed (%)	Total no. of tablets (%)	p value
Weekly	606 (97.12)	18 (2.88)	624(100)	<0.01
Daily	3810 (94.07)	240 (5.93)	4050(100)	

Figures in parenthesis indicate percentages

all the ADRs were more in the daily group compared to weekly group. However, the difference was only significant for abdominal pain and metallic taste ($p<0.01$ and 0.02 respectively) by Chi square test. The proportion of subjects reporting at least one ADR was also more in the daily group compared to the weekly group and this difference was also found to be significant ($p<0.01$) by Chi square test [Table 4].

Compliance for weekly regimen was found to be better when compared to that of the daily regimen and this difference was also found to be significant ($p<0.01$) by Chi square test [Table 5].

Discussion:

These were no significant differences with respect to the food consumption patterns between the daily and weekly regimen groups. Also, the selected subjects were randomly allocated into the weekly and daily regimen groups. Thereby the confounding effects of food habits, drugs, comorbidities etc., were ensured to be minimum. In weekly group, the mean hemoglobin value increased from 10.10 ± 1.25 g/dl before intervention to 11.02 ± 1.31 g/dl after intervention. In daily group it increased from 9.76 ± 1.35 g/dl to 11.68 ± 1.46 g/dl. Both these increases were found to be statistically significant ($p<0.05$). The mean increase in hemoglobin in weekly group was 0.91 g/dl and in daily group was 1.92 g/dl. This

difference was found to be statistically significant ($p<0.05$) Hence, the daily iron folic acid therapy was found to be more effective in increasing hemoglobin when compared to weekly group. Zavaleta et al. have also noted that hemoglobin levels improved significantly in both the iron supplementation groups (daily and intermittent-2days/week) compared to placebo group ($p<0.05$) and daily supplements led to higher Hb increases than intermittent supplements ($p<0.05$).^[5] However Shobha et al., have noted that there was no significant difference in the increase in hemoglobin levels between daily and twice weekly-supplemented subjects. The probable reasons for the difference could be differences in the sociocultural characteristics of the study subjects and also age groups (the subjects in the latter study were between 13-15 years in comparison to 15-45 years in our study).^[18]

Abdominal pain was the most common ADR in the daily group and abdominal pain and nausea were the most common ADRs in the weekly group. Incidence of all the different types of ADRs were more in the daily group compared to weekly group. However, the difference was only significant for abdominal pain and metallic taste. The proportion of subjects reporting at least one ADR was also more in the daily group compared to the weekly group and this difference was

also found to be significant. Shobha et al., have also noted that abdominal pain was the most common side effect in both daily and intermittent group, and incidence of all the different types of ADRs were significantly more in the daily group compared to weekly group.^[19] Joshi et al., have also observed similar findings though the difference was not significant.^[20]

Compliance for weekly regimen was found to be better when compared to that of the daily regimen and this difference was also found to be significant. Joshi et al., and Hyder et al., have also noted similar findings.^[20,21]

The limitations of the study were that it was based on a single urban poor locality of Bengaluru and hence the findings cannot be generalized to the entire city, state or country.

Conclusions:

Both daily and weekly IFA regimens can lead to significant rise in Hemoglobin levels in the reproductive age group women. However, the increase was significantly more with daily regimen compared to weekly regimen. Hence daily regimen seemed to be more effective in raising the hemoglobin levels. Incidence of all the different types of ADRs were more in the daily group compared to weekly group. However, the difference was only significant for abdominal pain and metallic taste. Compliance for weekly regimen was found to be significantly better when compared to that of the daily regimen.

Declaration:

Funding: Nil

Conflict of Interest: Nil

References:

1. Worldwide prevalence of anaemia 1993–2005. Geneva (Switzerland): WHO/CDC.c2008-[cited 2020 Jul 28]. Available from: https://apps.who.int/iris/bitstream/handle/10665/43894/9789241596657_eng.pdf;jsessionid=84C92153934D911E117F877F8AC9B202?sequence=1.
2. India factsheet NFHS-4. Mumbai: International Institute for population sciences. c2016-[cited 2020 Jul 14]. Available from: <http://rchiips.org/NFHS/pdf/NFHS4/India.pdf>.
3. Iron deficiency anaemia assessment, prevention, and control: a guide for programme managers. Geneva (Switzerland): WHO/UNICEF/UNU. c2001-[cited 2020 Jul 28]. Available from: http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf.
4. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. *J Nutr* 2001;131(2S-2):568S–579S.
5. Viteri FE, Berger J. Importance of pre-pregnancy and pregnancy iron status: can long-term weekly preventive iron and folic acid supplementation achieve desirable and safe status? *Nutr Rev* 2005;63(12):S65–S76.
6. Controlling iron deficiency-Nutrition Policy Discussion Paper No. 9. Geneva (Switzerland): Administrative Committee on Coordination/Subcommittee on Nutrition. c1991-[cited 2020 Jul 28]. Available from: https://www.unscn.org/layout/modules/resources/files/Policy_paper_No_9.pdf.
7. Agdeppa AI, Schultink W, Sastroamidjojo S, Gross R, Karyadi D. Weekly micronutrient supplementation to build iron stores in female Indonesian adolescents. *Amer J Clin Nutr* 1997;66(1):177–183.
8. Efficacy of intermittent iron supplementation in the control of iron deficiency anemia in developing countries: an analysis of experience. Toronto (Canada): Beaton GH, McCabe GP.c1999-[cited 2020 Jul 28]. Available from: <https://idl-bnc-idrc.dspacedirect.org/bitstream/handle/10625/29662/117067.pdf?sequence=3>.
9. Wright AJ, Southon S. The effectiveness of various iron supplementation regimens in improving the Fe status of anemic rats. *Brit J Nutr* 1990;63(3):579–585.
10. Viteri FE, Liu X, Tolomei K, Martín A. True absorption and retention of supplemental iron is more efficient when iron is administered every three days rather than daily to iron-normal and iron-deficient rats. *J Nutr* 1995;125(1):82–91.
11. Casey GJ, Jolley D, Phuc TQ, Tinh TT, Tho DH, Montresor A, et al. Long-term weekly iron-folic acid and de-worming is associated with stabilised haemoglobin and increasing iron stores in non-pregnant women in Vietnam. *PLoS One* 2010;5(12):e15691.
12. Vir SC, Singh N, Nigam AK, Jain R. Weekly iron and folic acid supplementation with counseling reduces anemia in adolescent girls: a large-scale effectiveness study in Uttar Pradesh, India. *Food Nutr Bull* 2008;29(3):186–194.

13. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional folate supplementation for preventing birth defects. *Cochr Data Systematic Rev* 2010;(12): Art. No.: CD007950.
14. Park K. *Textbook of Preventive and Social Medicine*. 25th ed. Jabalpur: BanarsidasBhanot publishers;2019.
15. Pallor: Epomedicine. c2020-[cited 2020 Jul 23]. Available from: <https://epomedicine.com/clinical-medicine/clinical-examination-pallor/>.
16. Key findings from NFHS-3. Mumbai: International Institute for population sciences. c2006-[cited 2020 Jul 14]. Available from: <http://rchiips.org/nfhs/factsheet.shtml>
17. Thomas MH, Bingham KC, Simmons WK. An evaluation of the HemoCue for measuring haemoglobin in field studies in Jamaica. *WHO Bull* 1994; 72(3): 423-426.
18. Zavaleta N, Respicio G, Garcia T. Efficacy and Acceptability of Two Iron Supplementation Schedules in Adolescent School Girls in Lima, Peru. *J. Nutr* 2000; 130(Suppl 2S): S462–464.
19. Shobha S, Sharada D. Efficacy of twice weekly iron supplementation in anemic adolescent girls. *Ind Ped* 2003; 40(12): 1186-1190.
20. Joshi M, Gumashta R. Weekly Iron Folate Supplementation in Adolescent Girls – An Effective Nutritional Measure for the Management of Iron Deficiency Anaemia. *Glob J Health Sci* 2013; 5(3): 188-194
21. Hyder SM, Persson LA, Chowdhury AM, Ekström EC. Do side-effects reduce compliance to iron supplementation? A study of daily- and weekly-dose regimens in pregnancy. *J Health Popul Nutr*. 2002; 20(2): 175-9.