ARTICLE

Weekly vs Daily Iron and Folic Acid Supplementation in Adolescent Nepalese Girls

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Objective: To compare the effectiveness of weekly vs daily iron and folic acid supplementation for control of anemia in adolescent Nepalese girls.

Design: Randomized controlled trial.

Setting: A Government Girl School in Dharan, Nepal, an urban foothill town that is 305 m above sea level.

Subjects: Consecutive healthy adolescent girls (n=209, median age 15 years) randomized to 3 groups matched for age, anthropometry, and personal and sociodemographic characteristics. Of 209 subjects, 181 completed the trial. Two girls had adverse reactions to treatment and were excluded.

Intervention: Group A (n=70) received a 350-mg ferrous sulfate and 1.5-mg folic acid combination once daily for 90 to 100 days. Group B (n=67) received the tablet under supervision once a week for 14 weeks. Group C (n=72) did not receive any drugs.

Outcome Variable: Presupplementation and postsupplementation differences in prevalence of anemia and change in hematocrit.

Results: Prevalence of anemia (defined as hematocrit <36%) declined from 68.6% and 70.1% in groups A and B to 20% and 13.4%, respectively, postsupplementation ($P<.001$), whereas the prevalence in group C changed little (68.1% to 65.3%, $P=.81$). There was a significant rise in the mean hematocrit of both supplemented groups (group A, 32.9%±3.5% to 41.0%±5.6%, $P<.001$; group B, 33.2%±3.6% to 40.4%±4.9%, $P<.001$) but no appreciable change in controls (34.2%±2.9% to 34.1%±3.3%, $P=.91$). Net change in mean hematocrit in both the supplementation groups was comparable ($P=.57$).

Conclusions: The prevalence of anemia in adolescent Nepalese girls is high. Supervised iron and folic acid therapy once a week is an effective alternative to daily administration and helps lower the prevalence of anemia in adolescent girls.

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ANEMIA IS the most prevalent nutritional problem worldwide, due mainly to iron deficiency. Its prevalence is highest among young children and women of childbearing age, particularly pregnant women.[1] The exact figure for global prevalence of anemia among adolescent girls is not known but is estimated to be quite high. The physiological growth spurt, with its attendant rise in mean hemoglobin level, and menarche cause an increase in daily iron requirement, which, if not met, can rapidly result in anemia. Diagnosis and treatment of anemia is of particular importance in adolescent girls because they enter the reproductive cycle soon after menarche. Even a marginal iron deficiency at this stage can precipitate severe anemia later on due to the stress imposed by pregnancy and parturition. Adolescent girls can be easily approached through school-based intervention programs.[2]

Based on study in rats, it has been suggested that iron supplementation should not be given daily, but rather weekly or twice weekly.[3] With a daily dose, the intestinal mucosal cells get saturated quickly,

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and iron absorption stops. Because the turnover rate of these cells is 5 to 6 days, a single weekly dose may be as efficacious and more cost-effective. Compliance might also improve because fewer doses of iron would be needed. This hypothesis has been supported by studies comparing the effectiveness of hemoglobin or hematocrit response, which was found to be similar regardless of whether supplementation was daily, weekly, or twice weekly.[2,4-7] To the contrary, Cook and Reddy[8] concluded that there is no significant absorptive advantage in giving iron less often than once daily. Hallberg[9] reiterated that there is no evidence that weekly

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SUBJECTS AND METHODS

STUDY POPULATION

The study was conducted in the Government Girl School of the Dharan Municipality, Nepal, from March 1998 to March 1999. The school caters to families from the lower-middle socioeconomic group. Dharan is a small foothill town (305 m above sea level) located more than 500 km east of Kathmandu. All girls from grades 8 to 12 between ages 11 to 18 years (N=225) were initially enrolled.

HISTORY AND EXAMINATION

The girls were questioned and examined by B.K.S.; a detailed sociodemographic profile was obtained, including the parents' education and occupation, type of housing, water supply, and toilet facilities. Type of diet (vegetarian or nonvegetarian), history of passage of worms, and menarchal status were recorded. Presence of pallor, icterus, edema, hyperpigmentation, lymphadenopathy, platynychia, bleeding spots, xerophthalmia, and goiter were recorded on a predesigned form. Physical examinations were conducted to rule out any systemic abnormalities. Weight, height, and mid-arm circumference were measured using standard techniques.[10] Girls suffering from any chronic illnesses (eg, asthma, rheumatic heart disease) or receiving any long-term allopathic or indigenous drug treatments were excluded from the study. Similarly, girls who had been hospitalized for any severe illness within the past 2 weeks were also excluded. Finally, 209 girls (median age, 15 years) were included in the study. The baseline hematocrit of each girl was estimated using the microhematocrit technique.

INTERVENTION

Subjects were randomly assigned to 1 of 3 groups: A (n=70), B (n=67), and C (n=72). Group A received supplementation with tablets containing 350 mg of ferrous sulfate and 1.5 mg of folic acid once a day for 90 to 100 days. The drug was given to the parents on a weekly basis, and they were asked to maintain a record of its consumption. An investigator (B.K.S) personally supervised administration of the same combination to group B on a fixed day once a week for 14 weeks. Group C served as a control and did not receive any medication. None of the participants received anthelmintics during the study period. The girls were not told whether they were anemic or not during the study period. Girls in the control group who were found to be anemic were offered therapy after the study was completed. Subjects who complained of abdominal pain and other gastrointestinal adverse effects were reassured about the harmless nature of the tablets. A few girls whose symptoms persisted were asked to take the tablets after a meal. Those with severe persistent symptoms were asked to stop taking the drug.

REEVALUATION

Fifteen days after the end of the study period (100 days or 14 weeks), the remaining subjects were reevaluated by measuring their hematocrit. Dropouts were due to severe adverse effects, noncompliance to treatment, or nonavailability for the final hematocrit estimation (**Figure**). Although these girls may not have completed the intervention and reevaluation, they were still included in the analysis.

STATISTICAL METHODS

Prevalence of anemia was calculated per the World Health Organization cut-off of hematocrit less than 36% in adolescents. Girls who were anemic before supplementation but concluded with a hematocrit of 36% or more were labeled responders. Analysis was carried out using Statistical Product and Service Solutions (Chicago, Ill) software version 10.0 on a compatible PC. We used an intention-to-treat analysis[11] to eliminate the potential bias of excluding girls who did not comply or were not available for follow-up. In this approach, all girls who were randomized remained in the denominator, and those for whom we did not have follow-up hematocrit values were considered to have final hematocrit values similar to their individual baseline values. Statistical tests including the χ^2 test, paired *t* test, analysis of variance, and Tukey test were performed. The level of significance was set at $P < .05$. Free and informed verbal consent of the subjects and their parents was obtained prior to recruitment in the study.

supplementation better prevents iron deficiency because the fundamental argument in its favor, that daily supplementation causes a mucosal block, is not valid.

The aim of this study was to investigate whether supervised weekly iron and folic acid supplementation would lower the prevalence of anemia and improve hematocrit status as effectively as daily supplementation in adolescent Nepalese girls, in whom baseline prevalence of anemia is suspected to be quite high.

RESULTS

Overall baseline prevalence of anemia was 68.8% (144/209). Sample hematocrits ranged from 24% to 42%, and none of the girls was severely anemic. Age-wise prevalence of anemia was 76.9% (10/13), 70.1% (47/67), 63.6% (42/66), and 71.4% (45/63) in the age categories of 12 or fewer, 12.01-14, 14.01-16, and more than 16 years respectively (*P*=.69). The mean hematocrit in these age categories was also comparable (mean±SD, 33.4%±3.4%, 33.6%±2.9%, 33.6%±3.7%, and 32.9%±3.5%, respectively; 1-way analysis of variance; *P*=.65). Prevalence of anemia in premenarchal vs postmenarchal girls was 72.7% (24/33) and 68.2% (120/176) (*P*=.60), with mean hematocrit of 33.4%±3.2% and 33.4%±3.4%, respectively (*P*=.99). The demographic characteristics of study groups indicated that all the groups were matched prior to supplementation (**Table 1**). The baseline prevalence of anemia and mean hematocrit in the 3 groups was also comparable (**Table 2**).

Of 209 girls evaluated initially, 28 girls were excluded at the end of the study (Figure). Two girls in group A had severe gastrointestinal problems that necessitated their exclusion from the study. The number of dropouts due to noncompliance was 8 (11.4%), 4 (6%), and 4 (5.6%), respectively, in the 3 groups. At the end of the

study, another 10 girls (2, 6, and 2 subjects in groups A, B, and C, respectively) were not available for repeat hematocrit estimation. Reevaluation was carried out in 58, 57, and 66 girls in the 3 groups, respectively.

Prevalence of anemia, which was matched in the 3 groups before supplementation, dropped considerably and to an equal extent in both supplementation groups ($P<.001$), but little change was observed in the control group ($P=.81$) (Table 2). Following supplementation, no difference was observed in the prevalence of anemia between the 2 supplemented groups ($P=.30$), whereas both groups were markedly different from controls ($P<.001$). A significant rise in mean hematocrit levels was documented in both intervention groups following supplementation ($P<.001$); no rise was observed among controls ($P=.91$). Postsupplemental hematocrit was not significantly different between groups A and B ($P=.73$). However, these values were significantly higher than the controls ($P<.001$). Net change in hematocrit was also similar in the 2 intervention groups ($P=.57$) and was markedly more than in controls ($P<.001$).

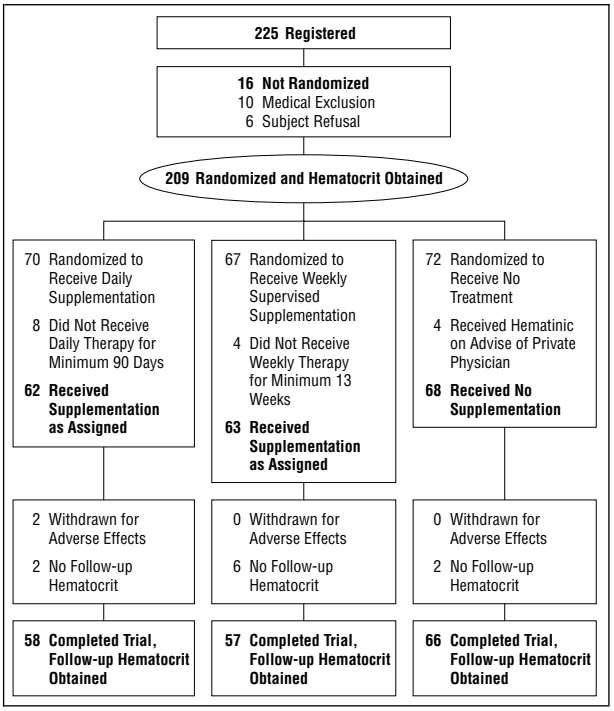
The number of responders and the mean hematocrit change were significantly higher in the 2 intervention groups than in controls ($P<.001$) (**Table 3**). Among responders, hematocrit rise was marginally more ($P=.04$) in the daily supplemented group as compared with those given weekly therapy. In the control group, more than 50% of subjects were true nonresponders (anemic both at baseline and 3 months thereafter) as compared with a much lower percentage in groups A and B. Whereas approximately 11% of girls slipped from being healthy to anemic in the unsupplemented group, only 1 girl in the supplementation groups went from healthy to anemic.

Further analysis did not reveal a significant relationship between means of initial hematocrit, postsupplementation hematocrit, or net change in hematocrit with age or menarchal status (1-way analysis of variance; $P>.05$). Mean hematocrit change in the responders was also not found to be influenced by the age or menarchal status of the subjects in different groups (3-way analysis of variance; all 2-way and 3-way interactions insignificant at 5% level).

COMMENTS

The prevalence of anemia in this study was extraordinarily high but matched closely with a few studies from the Indian subcontinent.[12,13] This was in sharp contrast to studies in other parts of the world, where the prevalence of anemia in adolescent girls ranges from 4% to 30% (Norway 4%, United States 5.9%, England 10.5%, Kuwait and Peru 25%-30%).[14-18] A detailed dietary history would have enabled further discussion on probable causes of the high prevalence in our sample.

The concept of a close association between anemia and iron deficiency is closest to correct when the prevalence of iron deficiency is high.[1] Therefore, it was safe to assume that iron deficiency was the principal cause of anemia and experiment with various modalities of iron supplementation. The effect of hematinic supplementation indicates that most girls had nutritional anemia, and other diagnoses may have contributed little to the etiology. A high



Study protocol.

prevalence of anemia also justified our blanket approach of treating all girls in intervention groups with supplements irrespective of their iron or hematocrit levels.

The dose and duration of iron therapy in the present study aligned with standard recommendations. The Centers for Disease Control and Prevention advocates 60 to 120 mg of elemental iron a day for 2 to 3 months to treat anemia in adolescent girls.[1] In the Indian subcontinent, folic acid is routinely added to iron tablets in current national programs for control of anemia.[19] Hematocrit levels in groups supplemented with daily and weekly iron and folic acid improved to an equal extent but significantly more than the controls following 3 months of supplementation. A follow-up period of 6 to 9 months would have helped to document the long-term effects of supplementation.

While refuting the mucosal block theory, Hallberg[9] also questioned the methodology and design of studies suggesting a similar hemoglobin response to weekly and daily iron administration. The controversy appears to have been put to rest by a recent meta-analysis of 22 completed trials on the efficacy of intermittent iron supplementation in control of iron deficiency anemia in developing countries.[20] Beaton and McCabe[20] concluded that both daily and weekly iron supplementation schedules are efficacious. Weekly iron supplementation is likely to be less effective than daily administration except in situations where supervision is feasible with weekly but not daily schedules. We proved that supervised weekly iron supplementation is as effective as daily administration but could not comment on a situation where weekly iron is given in an unsupervised manner. The question of whether there is a mucosal block appears redundant now, as field trials have provided ample evidence of the equal efficacy of weekly and daily iron administration schedules.

Table 1. Personal and Sociodemographic Characteristics*

	Mean ± SD			
	Group A† (n = 70)	Group B (n = 67)	Group C (n = 72)	*P* Value
Age, y	15.1 ± 1.7	15.1 ± 1.5	14.9 ± 1.8	.71
Weight, kg	42.3 ± 6.6	43.5 ± 6.2	42.8 ± 5.9	.55
Height, cm	150.2 ± 7.3	150.6 ± 6.5	149.5 ± 6.2	.59
Midarm circumference, cm	21.5 ± 2.2	21.6 ± 2.6	21.6 ± 2.2	.91
No. of family members	6.1 ± 2.2	6.4 ± 2.0	6.3 ± 2.3	.59
	No. (%)			
Achieved menarche	56 (80.0)	57 (85.1)	63 (87.5)	.46
Vegetarian	15 (21.4)	7 (10.4)	13 (18.1)	.21
History of worms	10 (14.3)	17 (25.4)	14 (19.4)	.26
Presence of				
Pallor	34 (48.6)	30 (44.8)	36 (50.0)	.82
Xerophthalmia	2 (2.9)	3 (4.5)	2 (2.8)	.82
Goiter	29 (41.4)	22 (32.8)	19 (26.4)	.16
Father's education				
Illiterate	4 (6.1)	3 (4.5)	4 (5.6)	.49
Up to high school	41 (62.1)	40 (59.7)	52 (72.2)	
High school graduate	21 (31.8)	24 (35.8)	16 (22.2)	
Father's occupation				
Unemployed	4 (6.2)	1 (1.5)	2 (2.8)	.15
Unskilled worker	18 (27.7)	30 (44.8)	32 (44.4)	
Skilled worker	43 (66.2)	36 (53.7)	38 (52.8)	
Mother's education				
Illiterate	19 (27.1)	14 (20.9)	19 (26.4)	.18
Up to high school	51 (72.9)	49 (73.1)	52 (72.2)	
High school graduate	0	4 (6.0)	1 (1.4)	
Mother's occupation				
Housewife	63 (91.3)	60 (89.6)	57 (79.2)	.07
Employed	6 (8.7)	7 (10.5)	15 (20.8)	
Housing				
Mud/thatch	21 (30.0)	29 (43.3)	26 (36.1)	.27
Brick/concrete	49 (70.0)	38 (56.7)	46 (63.9)	

*Almost all households consumed potable water and used house or community latrines. Between-group differences for means compared by 1-way analysis of variance; proportions, χ^2 test. Ellipses indicate not applicable.

†Fathers of 5 girls and mother of 1 girl in group A had died. Education status of the deceased father was not known in 4 cases.

Table 2. Impact of Hematinic Therapy on Prevalence of Anemia

	Group A Daily Supplementation (n = 70)	Group B Weekly Supplementation (n = 67)	Group C Control (n = 72)	*P* Value
Presupplementation				
No. (%) anemic*	48 (68.6)	47 (70.1)	49 (68.1)	.96
Mean hematocrit ± SD†	32.9 ± 3.5	33.2 ± 3.6	34.2 ± 2.9	.06
Postsupplementation				
No. (%) anemic*	14 (20.0)	9 (13.4)	47 (65.3)	<.001
Mean hematocrit ± SD†	41.0 ± 5.6	40.4 ± 4.9	34.1 ± 3.3	<.001
Net hematocrit change ± SD†	8.1 ± 6.0	7.2 ± 5.4	−4.2 ± 2.9	<.001

*Prevalence of anemia among the 3 groups compared with χ^2 test (presupplementation: A vs B, $P = .84$; A vs C. $P = .95$; B vs C, $P = .79$; postsupplementation: A vs B, $P = .30$; A vs C, $P < .001$; B vs C, $P < .001$). Within-group differences in prevalence of anemia presupplementation and postsupplementation analyzed with McNemar test (A, $P < .001$; B, $P < .001$; C, $P = .81$).

†Mean hematocrit among the 3 groups compared with 1-way analysis of variance (presupplentation: A vs B, $P = .85$; A vs C, $P = .06$; B vs C, $P = .19$; postsupplementation: A vs B, $P = .73$; A vs C, $P < .001$; B vs C, $P < .001$; net hematocrit change: A vs B, $P = .57$; A vs C, $P < .001$; B vs C, $P < .001$). Within-group differences in mean hematocrit presupplementation and postsupplementation anlayzed with paired *t* test (A, $P < .001$; B, $P < .001$; C, $P = .91$).

In developing countries, hematinic supplements are distributed through the primary health care systems. However, sustained efficacy is uncommon, owing to factors such as irregular tablet distribution and poor compliance. A less-frequent schedule would mean less cost and better compliance. Cook[21] argued against better compliance in the weekly group based on a dismal record of adherence to weekly programs for malarial prophylaxis. We

Table 3. Response to Hematinic Supplementation*

Response Category	Presupplementation vs Postsupplementation Status	Group A (n = 70)	Group B (n = 67)	Group C (n = 72)	Total (n = 209)	*P* Value: Between Groups	*P* Value: A vs B	*P* Value: A vs C	*P* Value: B vs C
Responders	Anemic to normal, No. (%)	35 (50.0)	38 (56.7)	10 (13.9)	**83 (39.7)**	<.001	.43	<.001	<.001
	Mean hematocrit change ± SD	12.6 ± 3.7	10.4 ± 4.0	4.4 ± 4.4	10.6 ± 4.6	<.001	.05	<.001	<.001
Nonresponders	Normal to normal, No. (%)	21 (30.0)	20 (29.8)	15 (20.8)	**56 (26.8)**	.37	.98	.21	.22
	Mean hematocrit change ± SD	6.3 ± 3.8	4.4 ± 4.4	−0.1 ± 2.2	3.9 ± 4.5	<.001	.24	<.001	.002
	Anemic to anemic, No. (%)	13 (18.6)	9 (13.4)	39 (54.2)	**61 (29.2)**	<.001	.41	<.001	<.001
	Mean hematocrit change ± SD	0.2 ± 0.6	0.2 ± 1.6	−0.5 ± 1.5	−0.3 ± 1.4	.15	.99	.26	.30
	Normal to anemic, No. (%)	1 (1.4)	0	8 (11.1)	**9 (5.3)**	...	...	...	...
	Mean hematocrit change ± SD	−5.0	...	−3.0 ± 1.1	−3.2 ± 1.2	...	...	...	...

*Between-group differences by group or response category compared with 2-way analysis of variance; all 1-way and 2-way interactions were significant ($P<.001$). Ellipses indicate not applicable.

What This Study Adds

Daily iron supplementation is a key strategy for short-term control of iron deficiency anemia. Control of anemia is particularly important in adolescent girls because they may be future mothers. A reduction in the frequency of iron supplement administration to once or twice a week is being examined in developing countries. If effective, this schedule would improve compliance and reduce costs.

The results of the present study indicate that weekly supervised iron and folic acid administration is an effective alternative to daily administration. In adolescent girls, weekly supplementation through school-based programs lowers the prevalence of anemia in areas with high prevalence of the disease.

think this problem can be obviated with a high degree of supervision, which is realistic and effective in school-based weekly iron supplementation programs.

Dropouts because of poor compliance were almost double in the daily supplementation group as compared with the weekly group, and persistent adverse effects were also limited to the daily supplementation group. However, because there were fewer subjects, the impact of a daily vs weekly schedule on the adverse effects of iron therapy could not be confidently demonstrated. Incidence of adverse effects could have been better analyzed if we had administered placebos to our control group. Also, we did not question the girls about their perceptions and preferences with regard to daily vs weekly therapy. It would be interesting to know whether girls liked a particular schedule, and if so, what their reasons were.

To conclude, the prevalence of anemia in Nepalese adolescent girls is quite high. To counter this, weekly supervised therapy is a good alternative to daily iron and folic acid administration. Weekly therapy appears to be equally effective yet causes fewer adverse effects, improves compliance, and reduces the cost of supplementation.

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