Is Weekly Iron and Folic Acid Supplementation as Effective as Daily Supplementation for Decreasing Incidence of Anemia in Adolescent Girls?

This clinical trial compared the effectiveness of weekly vs daily administration of iron plus folic acid for the treatment of anemia in adolescent Nepalese girls, a population with an extremely high prevalence of anemia. The study was conducted in a single government-run school in Dharan, an urban foothill town in Nepal. Girls from the 8th to 12th grades aged 11 to 18 years were enrolled. Baseline characteristics measured included sociodemographic variables, diet (vegetarian vs nonvegetarian), history of parasites, menarcheal status, anthropometrics, and presence of specific physical abnormalities. The baseline prevalence of anemia in this population was 69%. Subjects were randomized to 1 of 3 groups: group A (n = 70) 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; group B (n = 67) received the same combination on a fixed day once a week for 14 weeks, supervised by 1 of the investigators; and group C (n = 72) received no treatment during the study period. Of the 225 girls enrolled, 209 met inclusion criteria, and 181 completed the trial. The primary outcomes included prevalence of anemia (defined as hemoglobin <120 g/L), mean hemoglobin, and net change in hemoglobin for each group from baseline to 15 days after completion of therapy. The prevalence of anemia declined from 68.6% and 70.1% in groups A and B to 20.0% and 13.4%, respectively (P < .001). In group C, the control group, the prevalence went from 68.1% to 65.3% (P = .81). Mean hemoglobin and net changes in mean hemoglobin also increased significantly in both treatment groups compared with the control group. Increases in all outcomes between the daily and weekly observed treatment regimens were statistically equivalent.

We evaluated this study using standards of design, analysis, and results for therapeutic trials described in the “Users’ Guide” series published in the Journal of the American Medical Association. The focus is on the quality of the study, the validity of its results, and the generalizability of the outcomes.

QUALITY OF THE STUDY

Randomization of Subjects

The study was a randomized controlled trial. All students in grades 8 through 12 were initially enrolled, and 209 who met eligibility criteria were randomized. Though the authors state that subjects were randomly assigned to 1 of 3 groups, they do not state which method of randomization was used (eg, random number table). The resulting 3 study groups were roughly equivalent in size, and Table 1 from the study indicates that the demographic characteristics of the 3 groups were similar. These results suggest that, whichever randomization process was used, it was successful in creating 3 equivalent study groups. In the “Results” section, the authors state that all 3 groups were “matched” for age, anthropometrics, and personal and sociodemographic characteristics but do not state whether this was intentional matching in the formal epidemiological sense (ie, in order to control for bias in those factors involved in the match). Rather, it seems more likely that the groups were found to be matched on analysis, which is demonstrated by the fact that the 3 groups were statistically similar with regard to baseline characteristics (Table 1).

Accounting for Subjects

The authors account for all of the subjects in the study. Their text and figure clearly explain the reasons for the differences between the number originally registered (225) and the number eventually randomized (209). They state that 10 subjects met defined medical exclusion criteria and 6 refused participation. Of those randomized, 181 (87%) completed the trial, and reasons for loss of subjects are explicitly described (ie, severe adverse effects, noncompliance to treatment, and nonavailability for final hematocrit measurement). The authors indicate that they performed an “intention-to-treat” analysis. Intention-to-treat is the appropriate method of analysis to use for a randomized controlled trial because it presents the effect seen due to the treatment assigned, regardless of patient compliance or availability for follow-up.

Blinded Assessment

Ideally, therapeutic trials are double-blind. In this study, subjects were blind to whether they were anemic but not to their treatment assignment. Blinding subjects to their treatment assignment could have been accomplished if subjects in group B had taken placebo pills on the days they were not receiving their once-weekly combination of iron and folic acid and if subjects in group C had taken placebo pills every day. The authors state that incidence “of adverse effects [italics ours] could have been better...
analyzed if we had administered placebos to our control group” but do not address potential biases introduced by not blinding subjects to their treatment assignments. It is possible that subjects may have crossed over from one treatment group to another. For instance, because subjects in group A were not as explicitly supervised as those in group B, they may have been less conscientious about taking their medication daily, knowing that their friends were only taking their medication weekly. If daily administration of iron is more effective than weekly but many of the subjects in group A actually did not take iron daily, it may have biased the results against showing a difference.

The second component of double-blinding keeps the investigators from knowing subjects’ treatment assignments. Investigators were not blinded to treatment assignments in this study. However, it is unlikely that this significantly affected the results because the outcomes measured were relatively objective (ie, hematocrit values and a clear definition of anemia: hematocrit <36%).

VALIDITY OF RESULTS

Similarity of Groups

Table 1 indicates that groups A, B, and C were similar with respect to demographics, anthropometrics, menstrual history, past medical history, a variety of sociodemographic characteristics, and specific physical examination findings (ie, pallor, xeropthalmia, and goiter). Most importantly, the prevalence of anemia is similar among groups. The fact that these groups are similar, with respect to known prognostic factors, lends strength to the validity of the study results. Notably absent from baseline measures are indicators of iron deficiency (eg, microcytosis, serum ferritin, and free erythrocyte protoporphyrin). The authors comment that in a population with such a high prevalence of anemia, it can be assumed that iron deficiency anemia is the root cause. However, if iron deficiency was not evenly distributed among the 3 groups, it may have confounded the study results.

Equal Treatment of Groups

The major difference in treatment among groups was in documentation of compliance, though this was intentional. Direct observation of weekly therapy in group B assured compliance, whereas the compliance of group A with the daily regimen is unknown. If treatment were similarly observed in both groups and this lead to improved compliance in group A, it is possible that hematocrit levels in group A may have improved more than in group B.

Other possible differences in treatment among groups are not discussed. The use of additional vitamins or medications may have differed among the 3 groups. Additionally, the experience of the groups during the 15-day period after the trial prior to follow-up hematocrit evaluation may have differed. In both these situations, it is likely that any differences were offset through randomization, thus minimizing the possibility of bias.

Treatment Effect Size

The study found a dramatic decrease in the prevalence of anemia with the use of daily or weekly iron plus folic acid. All 3 groups had very similar rates of anemia at baseline (68%-70%). At follow-up, the control group had a similar anemia prevalence of 65.3%, whereas the intervention groups had rates of 20.0% and 13.4%, respectively. This equates to an absolute risk reduction of 45.3% for group A and 51.9% for group B. The number needed to treat for group A (daily supplementation) is 2.2. This means that for every 2 to 3 patients in group A treated for anemia, 1 will no longer be anemic. For group B (weekly supplementation) the number needed to treat is 1.92. For every 2 patients in group B treated for anemia, 1 will no longer be anemic.

Although the treatment effect of both regimens was impressive, the authors’ aim was to see whether supervised weekly iron and folic acid supplementation was as effective as daily supplementation. The ability of a study to demonstrate that 2 treatments are equivalent is based on its power. The authors do not discuss sample size calculations. They do not state a priori what magnitude of difference in effect size between daily and weekly regimens would be clinically important to detect. With sample sizes of 70 in group A and 67 in group B, this study has a 90% probability of detecting a difference of 25% or more. Thus, in this study there is a chance of a type II error (ie, failure to reject the null hypotheses that the 2 regimens are equally effective when they actually are not). If public health officials feel that a difference in treatment effect of less than 25% might be important, then this study lacks adequate power.

As mentioned previously, 2 of the difficulties with this study are the assumption that most patients with anemia had iron deficiency anemia and that ferrous sulfate and folic acid were supplied simultaneously. Because additional tests were not performed to confirm that the anemia was caused by iron deficiency, we cannot be certain that the reduction in anemia is directly due to the treatment introduced. Specifically, we do not know whether iron or folic acid supplementation is the primary reason for a reduction in the prevalence of anemia.

Treatment Effect Precision

Precision is usually expressed using confidence intervals. This study did not report confidence intervals for the binomial results of presence or absence of anemia post-treatment. The reduction in anemia in the 2 intervention groups was pronounced, and the P values were less than .001. This implies that there is a 99.9% confidence that these results were not due to chance alone.

GENERALIZABILITY

There are 2 issues of generalizability to consider in interpreting this study. The first is the appropriateness of applying the findings to other populations of adolescent girls in developing countries with high rates of anemia. It is important to recognize that this study was conducted in a single government school in a small foothill
town in Nepal. Whether the findings would be similar in larger samples of girls, in other regions of Nepal or other developing countries, and in non-school-based populations cannot be determined.

The application of the results of this study to adolescents in developed countries such as the United States is even more problematic. This population had a very high prevalence of anemia, as well as underlying medical conditions not commonly seen in the United States (eg, other nutritional deficiencies, parasitic infections, and goiter). The prevalence of iron deficiency in US adolescent girls is 9% to 11%, and the prevalence of iron deficiency anemia is 2% to 5%. Thus, the effect size that could be expected from empirical treatment of school-based populations of adolescent girls in this country with iron and folic acid would be far smaller.

**Application of Results to Individual Patients**

It is difficult to apply these results to individual patients in the United States. In addition to the differences in anemia prevalence and nutritional health, there is only limited evidence that early treatment of anemia in the adolescent US population can reduce morbidity. Trials from developing countries have reported conflicting results as to the benefit of iron supplementation on work productivity, psychomotor function tests, subjective well-being, and other outcomes. In addition, none of these studies have examined the benefits of treating mild cases of anemia, which were common in this current study.3

**Cost vs Benefits**

Iron supplementation is relatively inexpensive, and it may improve some clinical outcomes. The adverse effects of iron therapy include gastrointestinal symptoms, iron overload in patients with an underlying iron storage disorder, and the potential for an intentional or unintentional overdose, which can be fatal. Currently, the US Preventive Services Task Force states that “There is insufficient evidence to recommend for or against routine testing for anemia in . . . asymptomatic persons, but recommendations against such screening may be made on the grounds of low prevalence, cost, and potential adverse effects.”5 Routine screening of nonpregnant adolescents is not advocated by most organizations. Some organizations recommend screening for high-risk populations, such as adolescents with increased risk from heavy menses, weight loss, or nutritional deficits. The American Academy of Pediatrics currently recommends that hemoglobin or hematocrit be measured at least once for all menstruating adolescents, preferably at age 15 years.6

**CONCLUSIONS**

This study is a well-conducted clinical trial. It addresses a prevalent health problem in developing countries, and it demonstrates the effectiveness of an alternative treatment approach to anemia that may be advantageous in certain populations. The greatest limitation of this study is the relatively unique population that it employs. Nevertheless, public health officials interested in the treatment of anemia can potentially use this study to justify similar approaches in larger, more diverse populations.

Eliana Perrin, MD
Russell Rothman, MD
Tamera Coyne-Beasley, MD, MPH
Carol Ford, MD
Chapel Hill
W. Clayton Bordley, MD, MPH
Department of Pediatrics
University of North Carolina, Chapel Hill
Medical School, Wing C
CB No. 7225
Chapel Hill, NC 27599-7225
(e-mail: cbordley@med.unc.edu)

**REFERENCES**

2. Guyatt GH, Sackett DL, Cook DJ. Users’ guide to the medical literature, II: how to use an article about therapy and prevention, B: what were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA. 1994;271:59-63.