In a randomized controlled trial of iron fortification, anthelminthic treatment, and intermittent preventive treatment of malaria for anemia control of Ivorian children, only anthelminthic treatment shows modest benefit.

Rohner F et al; J Nutr 140: 635-641, 2010.

Introduction

Millions of African children suffer from anemia, which can be due to several different causes, including iron and/or other micronutrient deficiencies, malaria infections, intestinal helminth infections and hemoglobinopathies. Because of the broad range of possible causes of anemia, multiple intervention strategies need to be considered to minimize the disease burden.

Iron fortification of wheat flour has been adopted in Côte d'Ivoire and elsewhere to help control iron deficiency and iron deficiency-anemia. However, iron absorption from fortified foods depends on the amount and chemical form of iron added and the foods with which the iron is consumed. Moreover, iron absorption is decreased in the presence of inflammation, such as that caused by parasitic infection. Intestinal helminths, including hookworm, *Ascaris lumbricoides*, and *Trichuris trichiura* can cause anemia, both by causing intestinal blood loss and by inhibiting iron absorption secondary to systemic inflammation. Therefore, anthelminthic treatment (i.e., deworming) may also reduce the prevalence of anemia. Intermittent preventive treatment (IPT) for malaria also may decrease the prevalence of anemia in areas where malaria is endemic (see NNA January, 2010).

In this month's NNA, we summarize the results of a randomized, controlled trial comparing the efficacy of three interventions (iron fortification, anthelminthic treatment, and IPT), either alone or in combination, to reduce anemia among school-age children in Côte d'Ivoire.

Methods

The study employed a randomized, double-blind, factorial design, in which children were assigned to one of 8 groups (n = ~80/group) representing all possible combinations of iron fortification (F), anthelminthic treatment (H), IPT for malaria (M), and the respective placebos (P). Subjects were 554 school-aged children 6-14 years of age from a rural area in Côte d'Ivoire, a country which has mandated the addition of electrolytic iron to flour since 2007. Each child received either iron-fortified or unfortified (placebo) biscuits, anthelminthic treatment or placebo deworming pills, and IPT or placebo malaria treatment pills. The iron fortification groups received an additional ~20 mg/day of electrolytic iron 4 times per week (~3 times the estimated daily intake of iron from the national flour fortification program). The IPT groups received sulfadoxine-pyrimethamine (SP, as 500 mg sulfadoxine and 25 mg pyrimethamine) at baseline and 3 months. The anthelminthic groups received oral doses of albendazole (400 mg) and praziquantel (40 mg/kg) at baseline and 3 months.

Outcomes were measured at baseline and after 6 months of intervention. The primary outcomes were hemoglobin concentration and anemia prevalence. Iron status was measured using plasma ferritin (PF), transferrin receptor (TfR), and erythrocyte zinc protoporphyrin (ZPP). Infection was assessed by measurement of C-reactive protein (CRP) and alpha-1 acid glycoprotein (AGP). Malaria prevalence and parasitemia were measured using blood smears, and fecal samples were collected for egg counts for intestinal parasites (hookworm, *A. lumbricoides, T. trichiura,* and *S. mansoni*).

Results and conclusions

There were no differences in anemia prevalence, iron status, or parasite load among groups at baseline. The prevalence of anemia (hemoglobin <115 g/L) at baseline was 70%, and 28% of children had biochemical evidence of a concurrent infection (AGP >1.2g/L or CRP >10 mg/L). Overall, only 9% of children were iron deficient (PF <30 µg/L or TfR >8.5 mg/L and ZPP >40 µmol/mol heme), whereas 55% were infected with some type of helminth (mainly hookworm) and 58% were infected with Plasmodium spp.

In the PPP (all placebo) group, mean hemoglobin levels decreased and the prevalence of anemia increased during the 6-month intervention period. The prevalence of malaria infection decreased in all groups over the course of the study, possibly because of reduced transmission during the dry season, while TfR increased among all groups ($p<0.05$), indicating worsening iron status. Hookworm infection intensity (eggs per gram) decreased in groups that received anthelmintic treatment and increased in all other groups. Using multiple regression analysis, only the anthelminthic treatment had a modest positive effect on anemia, iron status, and hookworm infection intensity. The low prevalence of iron deficiency, type of iron fortificant, and seasonal decreases in malaria prevalence could explain the lack of effect of iron fortification and IPT on anemia, iron status, and malaria outcomes.

Program and Policy Implications

These results indicate that anthelminthic treatment may be an important strategy for anemia control in settings where intestinal parasites are highly prevalent. Where feasible, anemia control programs should be designed based on a preliminary assessment of the local causes of anemia. Large-scale iron fortification programs may not lead to changes in biochemical indicators of iron status if the initial prevalence of iron deficiency is low and/or if a poorly absorbed form of iron is used.

NNA Editors' comments*

This was a well-designed study that illustrates the challenges in implementing effective anemia control programs. Although more than two-thirds of the children were anemic at baseline, this was mostly mild anemia; and the prevalence of iron deficiency was quite low. By contrast, intestinal parasitic infections, especially hookworm infections, were common. More than one-fourth of the children demonstrated biochemical evidence of infection. The high initial prevalence of hookworm infection and the documented parasite response to anthelminthic treatment probably explains the positive impact of this form of treatment on change in hemoglobin concentration. Nevertheless, it would have been of interest to examine hemoglobin responses in relation to initial infection status and response to anthelminthic treatment.

The hemoglobin response to iron fortification programs depends on the initial prevalence and severity of iron deficiency, the amount of iron and the chemical form of iron used for the fortification program, and the presence of dietary factors and infections that may inhibit iron absorption. In view of the relatively low initial prevalence of iron deficiency in the study population and the fact that a poorly absorbable form of iron was used in the fortified food, it is not surprising that there was no detectable benefit of this intervention strategy. Updated recommendations for effective forms of iron for food fortification are now available (Hurrell, 2010).

The authors recognized the difficulty in assessing iron status in populations with high levels of infections, and they appropriately used several different methods to assess iron status. However, no information was provided on the concordance of the different indicators that were used, and several of the responses to intervention appeared to be inconsistent. Thus, additional analyses of the usefulness of these indicators of iron status under field conditions would be of interest.

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* These comments have been added by the editorial team and are not part of the cited publication.

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