Iron supplementation is unlikely to increase the incidence of infectious disease in children

Abstracted from: Gera T, Sachdev HPS. Effect of iron supplementation on incidence of infectious illness in children: systematic review. *BMJ* 2002; 325: 1142–1151.

BACKGROUND Anaemia is a major public health issue, affecting up to half of school age children in the world. Iron supplements can be administered using a range of methods, but the safety of supplementation remains uncertain. There are concerns that iron supplements may increase the risk of infectious disease, especially in developing countries.

OBJECTIVE To assess the relationship between iron supplementation and the incidence of infectious disease in children.

METHOD Systematic review with meta-analysis.

SEARCH STRATEGY The authors searched MEDLINE, the Cochrane Controlled Trials Register, HealthSTAR, IBIS, EMBASE, reference lists of identified studies, bibliographies and reviews and the proceedings of conferences and meetings. Experts and donor agencies were contacted for additional studies.

INCLUSION/EXCLUSION CRITERIA Randomised placebo-controlled trials were eligible if they assessed iron supplementation in children administered orally, through formula milk or fortified cereals or parenterally. Non-placebo-controlled trials of iron given parenterally were also eligible. Twenty-eight trials with 7892 children were included. Six were unpublished.

OUTCOMES Total recorded infectious illnesses; incidence of individual illnesses including respiratory tract infection, diarrhoea and malaria; positive smear for malaria.

MAIN RESULTS Iron supplementation did not increase the overall risk of infectious illness (incidence rate ratio 1.02, 95% CI 0.96 to 1.08) or the risk of developing specific diseases such as malaria. Iron supplementation was associated with an increased risk of diarrhoea, equivalent to about 0.05 episodes per child year (incidence rate ratio 1.11, 95% CI 1.01 to 1.23). Fortified foods may be the safest method of iron supplementation. There was significant unexplained heterogeneity between trials.

AUTHORS' CONCLUSIONS Iron supplementation is unlikely to increase the overall incidence of infectious illness in children, though it may increase the risk of developing diarrhoea.

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Commentary

Relevance

Gera and Sachdev address an important unresolved issue. Iron deficiency is the major micronutrient deficiency world wide. The international community have repeatedly called for action to correct this problem. Many countries have implemented strategies to increase iron consumption or supplement target groups. Safety has been a concern, particularly in malaria endemic areas. Gera and Sachdev conclude that providing extra iron does not increase the incidence of infections. These conclusions are consistent with those of another review of the risks and benefits of iron supplementation in malarious areas carried out by INACG in 1999.[1] Taken together, the findings suggest that iron supplementation is not associated with a significant increase in the risk of clinical malaria, although it increases the odds of being slide-positive for malarial parasitaemia at the end of the supplementation period.

Safety concerns are much broader than the incidence of infections, however. Absorption of orally administered iron is related to the degree of deficiency, which is translated in the number of intestinal iron receptors. Absorption is never completely 'switched off.' This means that there is a risk of iron overload for people carrying the haemochromatosis trait.[2] Until now, the importance of this factor has remained uncertain.

Iron is a potent free radical generator. Numerous mechanisms exist to protect against free radical damage.[3] Only when the balance between free radical generation and protection is upset does damage occur. The best known case is kwashiorkor.[4] Protective mechanisms may be enzyme-based, where minerals such as zinc, manganese and selenium are essential elements, or more indirect, using the electron scavenging properties of vitamins E and A, carotenes or polycyclic molecules (now referred to as antioxidants). Deficiencies of nutrients that act as antioxidants can compromise cell-mediated immunity. The varying responses to iron supplementation found by Gera and Sachdev could be attributed to a shortage of factors that protect against free radical damage when iron is present. Most of the above-mentioned micronutrients have also been implicated in decreased disease resistance in their own right.

Caveats

The authors have been methodologically rigorous and attempted to limit publication bias. As they note, however, there is wide statistical heterogeneity between studies. This heterogeneity is not surprising when one considers the important clinical and methodological variations among trials. Differences include setting, risk of infection, age range, route of administration, duration of iron supplementation and specificity of case definition.

Gera and Sachev modelled the heterogeneity using a random effects analysis. The relevance of pooling results from studies with such different characteristics is questionable. Some suggest that random effects analysis is simply a means of combining 'apples and pears.' Investigating sources of heterogeneity may be more informative than pooling.[5] The authors attempted to do this using stratified analysis and meta-regression. None of the study characteristics included in the meta-regression could explain the heterogeneity, although some important covariates such as dose or age group were not included.

On the other hand, the question of heterogeneity may not be so important. In the forest plot for incidence rate ratio of illnesses, the treatment effect is weak or non-existent in most of the individual studies. The treatment effect estimate is close to 1 for all of the big studies. Thus, the overall conclusion that iron supplementation is safe seems warranted.

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