Author’s response to reviews

Title: Effect of supplementation with ferrous sulfate or iron bis-glycinate chelate on ferritin concentration in Mexican schoolchildren: a randomized controlled trial

Authors:

Ximena Duque (xduquelo@hotmail.com)
Homero Martinez (homero@rand.org)
Jenny Vilchis-Gil (jennyben17@hotmail.com)
Eugenio Mendoza (eugenia.mo13@hotmail.com)
Sergio Flores-Hernandez (Sergio.flores@insp.mx)
Segundo Moran (segundomoran@hotmail.com)
Fabiola Navarro (fabisnava@hotmail.com)
Victoria Roque-Evangelista (vivevan_57@yahoo.com.mx)
Anayeli Serrano (yelina608@hotmail.com)
Robertino M Mera (rmm17189@live.com)

Version: 2
Date: 27 June 2014

Author’s response to reviews: see over
Mexico, D.F., June 24, 2014

Dr. Sandeep Prabhu
The Nutrition Journal Editorial Team

Dear Dr. Prabhu,

I am writing in response to your kind message dated June 2, 2014, in relation to the manuscript No. 2015169552121300, entitled “Effect of supplementation with ferrous sulfate or iron bis-glycinate chelate on ferritin concentration in Mexican schoolchildren: a randomized controlled trial”, co-authored by Ximena Duque, Homero Martinez, Jenny Vilchis-Gil, Eugenia Mendoza, Sergio Flores-Hernandez, Segundo Moran, Fabiola Navarro, Victoria Roque-Evangelista, Anayeli Serrano and Robertino M Mera.

Please find enclosed our reply to the Reviewers’ comments, accompanied by our revised manuscript. We have addressed both Major Compulsory Revisions as well as Minor Essential Revisions, referencing these in **bold** text, followed by our reply in *italics*. In the revised paper we have also formatted our replies in **bold italics**, for ease of reference.

On behalf of my co-authors, I want to thank the Editorial board, as well as the Reviewers, for your constructive critique, and hope you will find our replies satisfactory. In any case, we will be looking forward to your reply. Should there be any further issue that I should attend before our submission is ready for a new review, please let me know and I will take care of it at once.

With kind regards,

Homero Martinez, MD, PhD
Corresponding author
homero@rand.org
REPLY TO REVIEWER’S COMMENTS

We thank the Reviewer for the thoughtful and useful comments provided to the first version of this article. We have addressed all of her/his comments in the revised manuscript, and provide also an explanation about our responses in the following paragraphs. We have included the original comment in bold type, followed by our response in italics. The modified/addited text has also been incorporated into the revised manuscript using bold italics.

Major Compulsory Revisions

1. Discuss whether any strategies were employed to prevent contamination.

Supplementation was given daily during school days by project staff. Children were assigned randomly to receive supplementation with sulphate ferrous or iron bisglycinate chelate, and the person in charge of collecting the information kept a schedule and a registry of which child received the supplement, according to blinded assignment. Supplements were coded according to random assignment. In short, there was no chance for contamination to occur.

2. What was the a priori sample size, if any?

Sample size was calculated for a bioequivalence study (Blackwelder):

\[
n = \left( \frac{Z_{0.95} + Z_{0.80}}{2} \right)^2 \left( \frac{Ps(1-Ps) + Pn(1-Pn)}{(Ps-Pn-D)^2} \right),
\]

where Ps is probability of success with the standard treatment and Pn is probability of success with new treatment. Based on a previous study in which iron supplementation with ferrous sulfate was administered to reduce iron deficiency and anemia, the probability of success with the administration of iron sulfate was calculated as 0.81, while success with iron bis-glycinate was calculated as 0.86, we set the maximum allowable difference at no more than 0.1. The calculated sample size rendered 75 children per group, to which we added an additional 20% to consider attrition, for a final sample size of 90 children per group.

3. Was compliance measured and if so, how?

Compliance was assessed by means of the daily registration of supplement administration at school, according to the schedule kept by project staff responsible for its administration. For non-school days (i.e., weekends, holidays or days with no school attendance), parents were in charge of keeping the schedule, and to write down the administration of the assigned supplement. This same schedule included questions related to potential side effects.

4. Is it possible that diet in boarding schools is fairly constant among study participants and differences in the types of iron compounds may have had a greater effect difference if children were consuming different diets?

Diets in participating boarding schools are very similar, as the menus and food delivered are run from a central facility and standardized across participating schools. The fact that we found a lasting effect post-supplementation may be due to a sustained effect of iron intake, enough to maintain iron status once the initial deficit was overcome. Further, the effect of iron bis-glycinate chelate may be larger in presence of the typical Mexican diet (extended among families with low income), which includes
Phytates from cereals and legumes. These compounds bind iron, reducing its bioavailability for intestinal absorption. In a longitudinal study about iron deficiency due to consumption of low bioavailable iron diet in Africa by school children with normal iron status, the authors found after 15 months a mean change in total body iron stores of -142 mg, and estimated a 2% mean iron absorption of dietary iron. Haemoglobin decreased by 12 g/l and 75% of the cohort had deficit in tissue iron. The authors concluded that low iron bioavailability from legume and cereal–based diets is a cause of iron deficiency anaemia in children in rural Africa (Zimmermann).

5. Discussion does not address the broader implications and clinical relevance clearly. What conditions favour selection of one treatment over the other, such as resources, costs, availability, etc. Are both of these types of supplements readily available for use and which is more commonly used? Will these results change practice? Would choice over one or the other be affected by real-life conditions that were controlled for in this study, such as infection?

The most widely available form of iron supplement, routinely used in the Mexican health care services, is ferrous sulfate. This compound, however, is used mainly as a form of treatment for iron deficiency anemia, and not as an intervention to prevent iron deficiency or as treatment for children with iron deficiency before reaching the anemic state. Our results support the efficacy of iron sulphate, in lower doses than those used for treatment, as a preventive intervention. However, we will caution against extended use especially in areas where malaria is endemic, until safety studies have been conducted. In these areas, the World Health Organization recommends to first treat the infection, and then to provide iron supplementation. Our study also showed that a low dose of iron, with any of the two forms of iron compounds studied, was effective in increasing iron stores, and that this effect was sustained at least for 6 months after the intervention stopped. This raises possibilities for public health interventions that address a preventive approach to iron deficiency anemia, although we stress that iron supplementation is no substitute for a balanced diet, and that in areas where parasitic infections are prevalent, these should be treated as part of a comprehensive approach to improve iron status. In other words, prevention and control of anemia are complex and, depending on the setting, may require the implementation of a wider set of control measures (Righetti).

Minor Essential Revisions

1. Page 15 of Discussion provides paragraph on studies on iron supplementation that focus on children with IDA - the relevance of this lit review is not clear in the Discussion. The authors need to contextualize how this information relates to interpreting their study findings.

The reviewer has reason on this comment, as the discussion on intermittent or daily supplementation in children with IDA is not a topic specific to our study. Therefore, we have excluded it from the Discussion. We have, instead, focused on results of comparing the effect of ferrous sulphate vs. iron bis-glycinate chelate on iron deficiency more than in iron deficiency anemia, when information about it was available.


Blackwelder WC. “Proving the null hypothesis” in Clinical Trials. Controlled Clinical Trials, 1982;3:345-353.