Effect of sodium iron ethylenediaminetetra-acetate (NaFeEDTA) on haemoglobin and serum ferritin in iron-deficient populations: a systematic review and meta-analysis of randomised and quasi-randomised controlled trials

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CRD summary
This review assessed the impact of sodium iron ethylenediaminetetra-acetate on haemoglobin and serum ferritin concentrations in iron-deficient populations. It concluded that significant increases occurred for both outcomes. Generally, this was a well-conducted review, but the reliability of the authors' conclusions is uncertain given possible publication bias, significant variation across studies and the robustness of the subgroup analyses.

Authors' objectives
To evaluate sodium iron ethylenediaminetetra-acetate (NaFeEDTA) on haemoglobin and serum ferritin concentrations in iron-deficient populations.

Searching
MEDLINE, the Cochrane Library, EMBASE, WHO Library and China National Knowledge Infrastructure were searched with no language restrictions up to 2007. Search terms were reported. Conference proceedings and reference lists were manually searched, and experts were contacted, to identify additional articles.

Study selection
Randomised or quasi-randomised controlled trials that compared sodium iron ethylenediaminetetra-acetate (NaFeEDTA) with placebo in iron-deficient populations, where iron deficiency was defined as serum ferritin concentrations less than 12μg/L, were eligible for inclusion. Excluded studies were those where: vitamin C or other anti-anaemic drugs were simultaneously administered; alternative iron preparations were compared; NaFeEDTA was compared with other iron salts; an ethylenediaminetetra-acetate complex not containing iron was compared with placebo. Outcomes included: concentrations of haemoglobin, serum ferritin, or adverse effects (serum zinc).

Interventions in included studies comprised NaFeEDTA-fortified condiments (soya fish, fish sauce and curry powder) or doses of iron ranging from 4.9 to 20.0mg/d; the majority of studies used less than 10.0mg/d. The duration of the intervention ranged from three to 24 months. Included studies focused on children, women of child-bearing age and the general population; they were conducted in China, Vietnam or South Africa.

Two reviewers independently selected studies for inclusion in the review, with disagreements resolved by discussion or where necessary, through consultation with a third reviewer.

Assessment of study quality
Two reviewers independently assessed the studies for validity using criteria based on the Cochrane Effective Practice and Organisation of Care Group (EPOC) checklist describing: allocation concealment; follow-up; baseline measurement; blinded outcome assessment; reliable outcome measures; and contamination. Studies were defined as 'unacceptable' if more than three criteria were not completed. Disagreements were resolved by discussion or where necessary, through consultation with a third reviewer.

Data extraction
Two reviewers independently extracted the mean difference and 95% confidence intervals (CIs) for each outcome. Disagreements were resolved by discussion or where necessary, through consultation with a third reviewer.

Methods of synthesis
Pooled weighted mean differences (WMDs) and their 95% confidence interval were calculated using a random-effects model using the inverse variance method. Heterogeneity was assessed using the $X^2$ and $I^2$ tests. For haemoglobin outcomes, subgroup analysis was used to explore differences between baseline haemoglobin concentration (less than
120g/L or at/above 120g/L) and intervention doses (less than 10mg/iron/d or at/above 10mg/iron/d). For cluster randomised controlled trials with unit of analysis error, effective sample size was computed using the design effect, from which approximately adjusted effect estimates and standard errors were obtained; sensitivity analyses assessed the impact of excluding cluster randomised trials with unit of analysis error. Publication bias was assessed using Egger and Begg tests.

Results of the review
A total of seven studies (n=7,000 participants, range 152 to 4,479) were included in the review. Allocation concealment was undertaken in four studies, but was unclear in two; the methodological quality of all studies was termed 'acceptable'. No publication bias was detected.

Sodium iron ethylenediaminetetra-acetate (NaFeEDTA) significantly increased concentrations of both haemoglobin (WMD 8.56g/L, 95% CI 2.21 to 14.90; six studies) and serum ferritin (WMD 1.58g/L, 95% CI: 1.20 to 2.09; four studies), but not serum zinc (one study). Significant heterogeneity was present for all outcomes.

For subgroup analyses a lower baseline haemoglobin level was associated with a greater increase in haemoglobin concentration: baseline haemoglobin less than 120g/L (WMD 13.23, 95 % CI: 6.50, 19.95) versus haemoglobin at/above120g/L (WMD 2.53, 95% CI 1.01 to 4.04); other comparisons were not significant.

Authors' conclusions
For iron-deficient populations, sodium iron ethylenediaminetetra-acetate significantly increased concentrations of both haemoglobin and serum ferritin.

CRD commentary
The review question and inclusion criteria were clear. A thorough search for studies with no language restrictions was undertaken, which reduced the likelihood of language bias. There was no apparent search for unpublished studies, so some studies may have been missed. Publication bias was assessed and none detected, but given the small number of included studies, this finding should be interpreted with caution. All stages of the review process were undertaken in duplicate, reducing the potential for error and bias. Appropriate criteria were used to assess the quality of the included studies, which were defined as 'acceptable'. Allocation concealment was undertaken in four studies; it was unclear in two and not performed in one, although the authors explored the impact of this through sensitivity analysis and found that it did not impact upon the results.

Appropriate methods were employed for the meta-analysis, with suitable methods undertaken to assess statistical heterogeneity. A significant amount of between-study heterogeneity was detected and sub-group analyses were used to explore potential sources but, given the small number of included studies, it is uncertain how robust these findings are. The authors acknowledged that there may be issues of generalisability in extrapolating the results to cereal products.

This was generally a well-conducted review and the authors' conclusions appeared to follow from the data presented. However, the reliability of the findings is uncertain given the possibility of publication bias, significant variation across studies and the robustness of the subgroup analyses.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that comparisons of NaFeEDTA, and other commonly used iron preparations (such as iron sulphate - FeSO₄), should be addressed in future systematic reviews.

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