Short-term benefits and risks of intravenous iron: a systematic review and meta-analysis
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CRD summary
The review concluded that treatment with intravenous (IV) iron over a 60-day period may increase reticulocyte count and ferritin levels in comparison with oral administration or no iron. The use of nondextran IV iron may also increase haemoglobin and haematocrit levels. However, the uncertainty about between-study differences means that the reliability of the authors' conclusions is unclear.

Authors' objectives
To assess whether intravenous (IV) iron is more effective at stimulating erythropoiesis than oral iron over a period of 60 days, and to evaluate the safety of IV iron.

Searching
MEDLINE (from 1966), EMBASE (from 1974), CINAHL (from 1982), LILACS (from 1982), Web of Science (from 1979), Biological Abstracts (from 1985), the Cochrane Library, and abstracts from haematology and nephrology conference proceedings were searched to 2006; the search terms were reported. In addition, relevant journals were handsearched and authors of identified studies and pharmaceutical companies were contacted. The reference lists of retrieved studies were screened for relevant publications. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing any type of IV iron with enteral/oral or no iron treatment were eligible for inclusion. Studies allowing the use of recombinant endogenous erythropoietin (EPO) were also eligible for inclusion. Studies combining treatments with autologous blood donations or evaluating different doses of IV iron were excluded. The included studies used iron dextran, iron sucrose, iron saccharate and iron gluconate; the comparators were oral administration, placebo or no iron. Details of the doses and regimens of iron were reported. The majority of studies used recombinant EPO.

Participants included in the review
Studies of adult men and nonpregnant women, including participants of pre-operative status, healthy, or with chronic or critical illness, were eligible for inclusion. The included studies included participants with chronic renal failure (CRF), pre-dialysis CRF patients, those with chemotherapy-related anaemia, patients with inflammatory bowel disease, post-operative coronary artery bypass graft patients, pre-operative patients for elective surgery, as well as healthy patients.

Outcomes assessed in the review
Studies assessing efficacy and safety end points were eligible for inclusion. Efficacy end points included changes in haemoglobin (Hb), haematocrit (Hct), reticulocyte counts, transferrin saturation, ferritin, percentage of patients transfused and EPO dose. Safety end points included frequency of allergic reactions, haemodynamic reactions and infections. End points were to be assessed within 60 days.

How were decisions on the relevance of primary studies made?
Four reviewers independently assessed studies for inclusion.

Assessment of study quality
Validity was assessed using criteria based on recommendations by Chalmers et al., Moher et al. and Jadad et al. (references given). Four reviewers independently assessed validity and resolved any disagreements through consensus.

Data extraction
The data were extracted using a detailed evaluative tool. The authors did not state how many reviewers performed the data extraction. Data were extracted for primary outcomes including levels of Hb, Hct and ferritin, reticulocyte count and transferrin saturation. Data were also extracted on allergic and haemodynamic reactions to the intervention. The standard mean difference (SMD) and 95% confidence interval (CI) were calculated. Authors were contacted regarding unclear or missing data. Individual patient data were also obtained for some trials.

Methods of synthesis

How were the studies combined?
The studies were pooled using a random-effects model. To pool data with Hb or Hct as an end point, the ‘effect-size’ concept was used. The same method was used when comparing studies with post-treatment Hb levels with those having an increase in Hb as an end point. Publication bias was assessed using Rosenthal's fail-safe N and by visual assessment of funnel plots.

How were differences between studies investigated?
Statistical heterogeneity between the studies was assessed using chi-squared and I-squared tests. Sensitivity analyses were conducted: these compared fixed-effect and random-effects models and different types of IV iron. Additional sensitivity analyses on unspecified variables of clinical interest were also performed.

Results of the review

Thirteen RCTs (n=3,202) were included.

Six studies described randomisation methods. Ten studies were open label. All studies poorly reported cointerventions and other care programmes. The methods used to assess adverse events were reported in 6 studies. None of the included studies reported mortality, incidence of acute respiratory distress syndrome, or change in dose of recombinant EPO as outcomes.

Tests suggested either some evidence of potential publication bias, or the results may be due to poorer study design of the smaller studies.

Efficacy of IV iron.

There were no statistically significant differences in Hb or Hct between IV iron groups and control groups using oral iron or no iron (10 studies, n=484; SMD 0.26, 95% CI: -0.06, 0.58, p=0.11). Sensitivity analyses also found no differences between groups for 3 studies (n=115) using iron dextran IV compared with oral administration or no iron (SMD 0.22, 95% CI: -0.97, 1.40, p=0.72), though there was evidence of heterogeneity between these studies (I-squared 88.8%). Six nondextran studies (n=359) found that iron sucrose and iron saccharate were more effective in increasing Hb and Hct levels than oral iron or no iron (SMD 0.27, 95% CI: 0.04, 0.51, p=0.02); there was no evidence of statistical heterogeneity between these studies.

The use of IV iron resulted in an increase in the reticulocyte count compared with the oral iron or no iron groups (6 studies, n=185; SMD 0.70, 95% CI: 0.10, 1.28, p=0.02), and an increase in ferritin (3 studies, n=102; SMD 1.18, 95% CI: 0.69, 1.68, p=0.00001), though there was evidence of statistical heterogeneity for these results (I-squared 70.4%).

There were no significant benefits from IV iron compared with oral or no iron for transferrin saturation (SMD -0.12, 95% CI: -1.19, 0.96).

Safety of IV iron.

It was not possible to pool data for allergic and haemodynamic reactions as most studies did not report these outcomes clearly. From the limited data available it was reported that IV iron caused more drug intolerance, but it is unclear whether it caused more serious adverse effects.

Authors' conclusions
The findings suggest that treatment with nondextran IV iron may be of benefit to a variety of patients.

**CRD commentary**
There was a clearly stated review question and clear inclusion criteria. Several appropriate sources were searched without language restrictions for published and unpublished studies, thereby minimising publication and language bias. Appropriate review methods were also used to minimise error and bias in the study selection and quality assessment processes, although it is unclear whether these methods were used for the data extraction. The exclusion of studies with unavailable raw data or limited sample sizes may mean that some relevant studies were missed. Statistical heterogeneity was assessed, though the source of the heterogeneity was not fully investigated. However, the studies included very different participant populations and there may well be clinical heterogeneity present; in view of this, the pooling of studies may not have been appropriate. In summary, the uncertainty about between-study differences means that the reliability of the authors' conclusions is unclear.

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

Research: The authors stated that further large RCTs are necessary to clarify the efficacy and safety of IV iron.

**Funding**
Fonds de Recherche en Soins Intensifs and Medecine Transfusionnelle of the Cite de la Sante de Laval.

**Bibliographic details**

**PubMedID**
17880619

**DOI**
10.1111/j.1537-2995.2007.01415.x

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anemia /drug therapy; Enteral Nutrition; Ferritins /metabolism; Humans; Infusions, Intravenous; Iron /administration & dosage /adverse effects /therapeutic use; Randomized Controlled Trials as Topic; Reproducibility of Results; Safety

**AccessionNumber**
12007003306

**Date bibliographic record published**
07/02/2008

**Date abstract record published**
30/09/2008

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.