Iron replacement therapy in inflammatory bowel disease patients with iron deficiency anemia: a systematic review and meta-analysis

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CRD summary
This review found small but significant benefits with intravenous administration of iron replacement compared to oral administration in patients with inflammatory bowel disease and iron deficiency anaemia. The authors acknowledged limitations in the evidence available and their cautious conclusions appear likely to be reliable.

Authors’ objectives
To evaluate the clinical efficacy of intravenously administered iron replacement compared to oral administration in adults with inflammatory bowel disease and iron deficiency anaemia.

Searching
MEDLINE, EMBASE, DARE, Web of Science, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched to January 2011 for relevant studies in English. Search terms were reported. Abstracts from the American Gastroenterology meeting Digestive Disease Week (2004 to 2011) and the European Gastroenterology meeting United European Gastroenterology Week (2004 to 2011) were handsearched for additional studies.

Study selection
Randomised controlled trials (RCTs) in which the efficacy of intravenous iron replacement was compared to orally administered iron replacement in adult patients with inflammatory bowel disease and anaemia from iron deficiency were eligible for inclusion. The primary outcome was the mean difference in haemoglobin. Other outcomes evaluated were ferritin levels, quality of life, measures of inflammatory bowel disease activity and adverse events. Studies that used crossover designs and studies that included patients concurrently using erythropoietin were excluded.

Patients in the included trials presented with mean baseline haemoglobin levels of 87g/L to 104.9g/L and mean baseline ferritin levels in the range 5μg/L to 14.0μg/L. Iron replacement was administered as a sulphate (4.2 to 38.4 ± 20g), in sucrose (1.4g to 1.7g) and in carboxymaltose (1.0g). Duration of treatment ranged from six to 20 weeks.

One reviewer conducted an initial broad screening of abstracts and two reviewers independently performed the study selection; any discrepancies were resolved by consensus.

Assessment of study quality
Two independent reviewers assessed methodological quality using the Cochrane Collaboration tool for the assessment of risk of bias in terms of sequence generation, allocation concealment, blinding of participants, personnel and outcomes, the reporting of incomplete outcome data, freedom from selective outcome reporting and other sources of bias. Any disagreements were resolved by discussion.

Data extraction
Data were extracted on an intention-to-treat basis by two independent reviewers and used to calculate odds ratios (OR) and mean differences for the outcomes and 95% confidence intervals for the estimates. Medians presented in the trials were accepted as being means. The reviewers contacted the trial authors for missing data where necessary.

Methods of synthesis
Pooled odds ratios, weighted mean differences (WMD) and 95% confidence intervals for the summary estimates were calculated using a random-effects model. Statistical heterogeneity was assessed using the I² test.

Results of the review
Three RCTs (333 participants, 46 to 196) were included in the review. Adequate randomisation was performed in all the trials. The allocation sequence was not concealed in one trial. The authors stated that there was no blinding of
participants or study staff in any of the trials, although study personnel were blinded to treatment allocation in one trial. Two trials presented all the data. Risk of bias was judged to be low for one trial and high for two trials. All the trials received financial support from the manufacturers of intravenously administered iron replacement.

Administration of iron replacement therapy by the intravenous route was associated with significant benefits compared to oral administration with higher haemoglobin levels (WMD 6.8g/L, 95% CI 0.9 to 12.7; I²=80%), serum ferritin (WMD 109.7μg/L, 95% CI 5.37 to 214; I²=99%) and fewer instances of discontinuation due to side effects (OR 6.2, 95% CI 2.2 to 17.1; I²=0%). The authors stated that the significant statistical heterogeneity observed in the results may be due to variations in duration of iron replacement therapy and follow-up.

There were no significant differences between groups in quality of life scores and disease activity.

**Authors' conclusions**
Intravenous administration of iron replacement therapy conferred significant benefits in haemoglobin and ferritin levels with fewer adverse events compared to oral administration in patients with inflammatory bowel disease and iron deficiency anaemia. However, the differences between administration routes was small and the clinical significance of the improvements was not clear. The total sample size was small and more trials were needed.

**CRD commentary**
The review addressed a clear question. Criteria for inclusion of studies were defined and reproducible. Appropriate databases were searched for relevant studies and there were attempts to identify unpublished studies. The restriction of the review to studies in English meant there was some risk of language bias. Steps were taken by the reviewers to minimise errors and bias at each stage of the review process. The methodological quality of the included studies was assessed. Most trials were judged by the reviewers to be at high risk of bias; one was classed as low overall risk of bias. High levels of statistical heterogeneity made it unclear whether pooling of the results was appropriate, particularly where there was variation in the duration of iron replacement therapy and follow-up.

The authors acknowledged the trial limitations of small sample sizes, reporting of data and the small improvements observed. Their cautious conclusions appear likely to be reliable.

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

**Research:** The authors stated that further trials with longer durations of post-infusion follow-up were necessary to ascertain whether the observed increases in ferritin levels were clinically significant. The cost-effectiveness of intravenous iron replacement therapy was not yet determined.

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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.