Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and meta-analysis

CRD summary
The review concluded that patients with chronic kidney disease on haemodialysis had a better haemoglobin level response when treated for anaemia with iron intravenously compared with oral administration, but the benefit was small for those not on dialysis. The authors’ conclusion reflected the evidence presented, but the differences between trials and the short follow-up period should be borne in mind.

Authors' objectives
To evaluate the effectiveness of intravenous iron supplementation compared with oral iron supplementation for the treatment of anaemia in patients with chronic kidney disease.

Searching
PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles in any language until January 2008; search terms were reported. Conference proceedings of the American Society of Nephrology and European Renal Association-European Dialysis and Transplant Association were searched between 2001 and 2007. Reference lists of included trials and reviews identified were scanned.

Study selection
Randomised controlled trials (RCTs) that compared oral iron preparations versus different intravenous iron preparations in haemodialysis and peritoneal dialysis patients and non-dialysis patients with chronic kidney disease were eligible for inclusion.

The primary outcome measure was absolute haemoglobin level or change in haemoglobin level from baseline after two to three months. Secondary outcomes were: all-cause mortality at trial end; cardiovascular morbidity and mortality; bacterial infections; adverse events; adverse events that required discontinuation of iron therapy; number of patients with chronic kidney disease who required renal replacement therapy; iron saturation and ferritin level; erythropoiesis-stimulating agent requirement; number of patients requiring hospitalisation; quality of life; and number of patients needing blood transfusions.

Interventions in the included trials were intravenous iron sucrose, iron gluconate, iron dextran and ferumatoxil. Comparators were oral iron sulfate, iron succinate, ferritin or iron fumarate. Regimens varied for both intravenous and oral iron drugs. Duration of treatment ranged from one week to six months. More than half the trials were of patients who had been on dialysis (mainly haemodialysis) for between 16 to 57 months. For the remaining patients not on dialysis, renal function was reported as glomerular filtration rate ranging from 12 to 32mL/min or creatinine clearance as 13 to 18.6mL/min. Baseline transferrin saturation and baseline erythropoiesis-stimulating agent dose varied widely between trials (where reported). The age of the participants ranged from 15 years to 66 years; the proportion of men ranged from 31.6 to 80% (where reported).

Two reviewer independently selected studies for inclusion.

Assessment of study quality
Two reviewers independently assessed trial validity using the following criteria: allocation concealment, generation of allocation sequence, and blinding. Allocation concealment and generation were graded as adequate, unclear or inadequate, based on guidelines in the Cochrane Handbook for Systematic Reviews of Interventions.

Data extraction
Data for each outcome were extracted and used to calculate the mean and standard deviations (SD) or relative risk (RR) and corresponding 95% confidence intervals (CIs). Data were stratified into two groups: patients on dialysis, and
patients with chronic kidney disease not on dialysis. Where necessary authors of included trials were contacted for missing data.

Two reviewers independently extracted data; disagreements were resolved by recourse to a third reviewer.

Methods of synthesis
Data were pooled using the DerSimonian and Laird random-effects model to produce weighted mean differences (WMDs) for continuous variables and relative risks for dichotomous data together with 95% confidence intervals. Heterogeneity was assessed using the $X^2$ test (with a threshold of $p<0.1$) and $I^2$ statistic (with a threshold of $>50\%$). Reasons for heterogeneity were explored using meta-regression analysis to assess the effect on the primary outcome of the following variables: baseline haemoglobin level; percentage of patients receiving erythropoiesis-stimulating agent and mean erythropoiesis-stimulating agent dose; intravenous iron dose; dialysis duration; and mean glomerular filtration rate.

A sensitivity analysis was conducted on the effect of allocation concealment and generation for the primary outcome.

Results of the review
Thirteen RCTs were included in the review (n=1,207 patients, but numbers in text and table differ; range 35 to 304). Eight RCTs reported adequate allocation generation. Four RCTs reported adequate allocation concealment. None of the trials were blinded. Follow-up was from 35 days to four months.

There was a significantly greater haemoglobin level increase for intravenous iron treatment compared with oral iron treatment for patients with chronic kidney disease on dialysis (WMD 0.83 g/dL, 95% CI 0.09 to 1.57; $I^2=89.9\%$; seven RCTs) and for those not on dialysis (WMD 0.31 g/dL, 95% CI 0.09 to 0.53, $I^2=40.6\%$; six RCTs). There was significant heterogeneity for the analysis of trials of patients on dialysis.

Overall, there were no significant differences between intravenous and oral treatment groups for: all-cause mortality (five RCTs; only three deaths occurred); adverse events (nine RCTs); severe adverse events and adverse events that required discontinuation of therapy (12 RCTs); or the need for blood transfusion (two RCTs; there were only five events). There were also no significant differences between treatment groups in the number of patients with chronic kidney disease not on dialysis requiring renal replacement therapy (three RCTs); there was no significant heterogeneity for this analysis. There were no data on cardiovascular morbidity or mortality, or bacterial infections.

Meta-regression showed significant associations between a larger effect estimate for haemoglobin level response and lower baseline haemoglobin level ($p=0.004$), lower erythropoiesis-stimulating agent dose ($p=0.002$) and greater intravenous iron dose ($p<0.001$) for trials of patients on dialysis.

Sensitivity analysis showed no significant difference between trials reporting adequate allocation concealment and allocation generation (two RCTs), and trials reporting unclear or inadequate methods (five RCTs).

Other results were also reported.

Authors' conclusions
The review concluded that patients with chronic kidney disease on haemodialysis therapy had a better haemoglobin level response when treated for anaemia with iron given intravenously compared with oral administration, but the benefit was small for chronic kidney disease patients not on dialysis.

CRD commentary
The review question was clear, with appropriate inclusion criteria. Several relevant sources were searched and efforts were made to reduce language and publication bias. Appropriate methods were used to reduce reviewer error and bias in the selection of studies, assessment of validity and extraction of data.

Trial quality was assessed using limited criteria; the results for each trial were reported. The statistical analysis appeared...
appropriate and reasons for heterogeneity were explored. The included trials reported only short-term outcomes (maximum three months follow-up). There was wide variation between trials in terms of treatment regimen and duration, outcomes and participants.

The authors’ conclusion reflected the evidence presented, but the differences between trials and the short follow-up period should be borne in mind.

**Implications of the review for practice and research**

**Practice:** The authors stated that the advantage on haemoglobin level response for patients with chronic kidney disease not on dialysis is minimal and should be weighed against the inconvenience and cost of intravenous iron treatment in patients who do not have an easy intravenous access. However, intravenous iron should be considered as an alternative for patients who cannot tolerate oral iron or have a persistent iron deficiency despite an adequate dose of oral iron.

**Research:** The authors stated that further well-designed large RCTs comparing intravenous iron with oral iron should be carried out, assessing clinical outcomes and common haematological parameters and including long term follow-up. Additional studies are required to evaluate more patients on dialysis (including peritoneal dialysis), as well as pre-dialysis populations. Subgroup analyses should be conducted according to patient age, comorbidity and baseline iron status.

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