Systematic Review and Meta-Analysis of Iron Therapy in Anaemic Adults Without Chronic Kidney Disease: Updated and Abridged Cochrane Review

Ben Clevenger [1], **Kurinchi Gurusamy** [1], **Andrew A Klein** [2], **Gavin J Murphy** [3], **Stefan D Anker** [4], **Toby Richards** [1 *]

[1] Division of Surgery and Interventional Science, University College London, London, UK

[2] Department of Anaesthesia and Intensive Care, Papworth Hospital, Cambridge, UK

[3]Department of Cardiovascular Sciences and NIHR Cardiovascular Biomedical Research Unit, University of Leicester, and Glenfield General Hospital, Leicester, UK

[4]Department of Innovative Clinical Trials, University Medical Centre Göttingen (UMG), Göttingen, Germany

***Corresponding author:**

Professor Toby Richards, Division of Surgery and Interventional Science, 4th Floor, UCL Medical School Building, 21 University Street, London, WC1E 6AU, UK

Email: toby.richards@nhs.net

Telephone: +44 (0)20 7679 2000

Fax: +44 (0) 20 7830 2245

Abstract

Aims

Anaemia is increasingly recognised as having an independent impact upon patient outcomes in cardiac disease. The role of novel iron therapies to treat anaemia is increasing. This systematic review and meta-analysis assesses the efficacy and safety of iron therapies for the treatment of adults with anaemia.

Methods and Results

Electronic databases and search engines were searched as per Cochrane methodology. Randomised controlled trials (RCTs) of iron versus inactive control or placebo, as well as alternative formulations, doses and routes in anaemic adults without chronic kidney disease or in the peri-partum period were eligible. The primary outcome of interest was mortality at one year. Secondary outcomes were blood transfusion, haemoglobin levels, quality of life, serious adverse events and length of hospital stay.

64 RCTs (including five studies of heart failure patients) including 9004 participants were included. None of the studies were at a low risk of bias. There were no statistically significant differences in mortality between iron and inactive control. Both oral and parenteral iron significantly reduced the proportion of patients requiring blood transfusion compared to inactive control (risk ratio (RR) 0.66 (95% confidence interval (CI) 0.48 to 0.90) and RR 0.84 (95% CI 0.73 – 0.97) respectively. Haemoglobin was increased more by both oral and parenteral iron compared to inactive control (mean difference (MD) 0.91 g/dL (95% CI 0.48 to 1.35) and MD 1.04 (95% CI 0.52 to 1.57) respectively), and

parenteral iron demonstrated a greater increase when compared to oral iron (MD 0.53 g/dL (95% CI 0.31 to 0.75)). In all comparisons there were no differences in the results comparing patients with and without heart failure.

Conclusion

Both oral and parenteral iron are shown to decrease the proportion of people who require blood transfusion and increase haemoglobin levels, without any benefit in mortality. Further trials at a low risk of bias, powered to measure clinically significant endpoints are still required.

** This paper updates the findings of a Cochrane review first published December 2014 in The Cochrane Database of Systematic Reviews (CDSR) Issue 12 (http://www.thecochranelibrary.com).*

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Keywords

Iron; Iron Therapy; Intravenous Iron; Iron Deficiency; Anaemia; Haemoglobin; Blood Transfusion; Patient Blood Management

Introduction

Anaemia has a high worldwide prevalence, and is estimated to affect 1.6 billion people worldwide.(1) The World Health Organisation (WHO) defines anaemia as a circulating haemoglobin concentration of <120 g/L in non-pregnant women and <130 g/L in men.(1)

Anaemia can cause fatigue and decreased work activity.(2) It has been shown to worsen heart failure (3) and is associated in increased mortality in people with chronic heart failure.(4) Anaemia is also associated with worse outcomes after cardiac and non-cardiac surgery, including increased mortality and hospital length of stay.(5, 6)

Approximately 50% of anaemia is due to iron deficiency.(1, 7, 8) Absolute iron deficiency can be caused by nutritional deficiency of iron, loss due to bleeding or decreased absorption of dietary iron, causing a lack of stored iron. Alternatively, a state of functional iron deficiency can occur, leading to iron restricted erythropoiesis despite normal iron stores. Functional iron deficiency can be caused by: defective incorporation of iron into developing red cells, decreased availability of iron stores as the result of increased uptake and retention of iron within the reticuloendothelial system or failure of absorption of intestinal iron due to inflammation, mediated by hepcidin. Chronic inflammation and disease may lead to increased hepcidin levels and thus anaemia of chronic disease.(9)

European Society of Cardiology guidelines recommend the diagnosis and treatment of correctable causes of anaemia in heart failure.(10) There has been considerable attention in cardiac disease on the role of iron therapy for iron

deficiency but the efficacy and effect of iron therapy to treat anaemia remains uncertain.

This review updates findings published in the Cochrane Database of Systematic Reviews in 2014,(11) to assess the safety and efficacy of iron therapies for the treatment of adults with anaemia who are not pregnant or lactating and do not have CKD. No previous systematic review had been performed to assess the clinical benefits of iron therapies excluding these groups. It is important that the effectiveness of iron can be explored in a wide range of clinical conditions and this review can influence the care of many patient groups. This is particularly important with the burgeoning interest in patient blood management. The increased awareness of the importance of detecting and treating anaemia and reducing unnecessary or inappropriate blood transfusions includes forthcoming National Institute of Health and Care Excellent (NICE) guidelines for transfusion.(12)

Methods

The Cochrane methodology was applied to this review.(11) Table 1 presents the inclusion and exclusion criteria of studies.

As per the *Cochrane Handbook for Systematic Reviews of Interventions* (13) all known relevant electronic databases and search engines were accessed. Searches were not restricted by language, date or publication status. The following databases were searched until November 2014: Cochrane Central Register of Controlled Trials *(The Cochrane Library)* (Issue 7, 2013), MEDLINE

(Ovid) (1950-), EMBASE (Ovid) (1980-), CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus (1957-), ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970-) and ISI web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990-). The reference lists of all included studies and previously published reviews were searched for additional studies. Search terms included: iron, ferrous, ferric, an(a)emia/c. Full details of the search strategy are available.(11)

Study selection

Iron therapy can be administered by a variety of routes and in different formulations.(20) Randomised controlled trials (RCTs) of iron (oral and parenteral) versus control or placebo, as well as alternative formulations, doses and routes, were eligible to be included in the meta-analysis. RCTs irrespective of blinding, language, publication status and date of publication, study setting and sample size were included. Any non-peripartum anaemic adults without chronic kidney disease were included in this review, irrespective of the setting and the degree of anaemia. The primary outcome of interest was mortality at one year.

Risk of bias was assessed as per the instructions of the Cochrane Handbook(13) according to the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and source of funding bias.

Two review authors (KSG and TR or BC) identified trials for inclusion independently of each other, listing excluded studies and the reason for exclusion. Differences were resolved by discussion.

Statistical Analysis

Meta-analyses were performed using the software package Review Manager version 5.3(18) and in accordance with the recommendations of the *Cochrane Handbook.(13)* The results of the random effects model were reported. The risk ratio (RR) with 95% confidence interval (CI) was calculated for dichotomous variables, and the mean difference (MD) with 95% CI or standardised mean difference (SMD) with 95% CI as appropriate for continuous variables. For time-to-event outcomes such as mortality at maximal follow-up, hazard ratio (HR) with 95% CI was calculated.

Subgroup analyses were performed for trials studying participants chronic heart failure compared to those without. Subgroup analyses were also performed in trials in which erythropoietin was used as a co-intervention versus those that did not, and by participant group: blood loss conditions, cancer, pre-operative, autoimmune and miscellaneous (See supplementary online appendix for these results). Test for subgroup differences within Review Manager was used, with a P value of <0.05 considered statistically significant.

Sensitivity analysis was planned to exclude trials with unclear or high risk of bias for random sequence generation; unclear or high risk of bias due to lack of blinding of participants, healthcare providers or outcome assessors; and unclear or high risk of bias due to incomplete outcome data. However, all trials had at

least one domain with unclear or high risk of bias. Sensitivity analysis was performed by excluding trials in which we imputed the mean and the standard deviation, when there were at least two trials for the outcome. (See supplementary online appendix for sensitivity analysis results).

Results

Study selection

Overall, 225 full text publications from 17693 citations were identified as potentially relevant studies and full text copies were retrieved and assessed. Exclusions are detailed in *Figure 1: Study selection flow diagram*. In total 128 publications describing 65 RCTs fulfilled the inclusion criteria. Duplicate reporting included the publication of conference abstracts prior to publication and publication of subset analysis, cost analysis and combined reporting.

Study characteristics

Overall, 9004 participants were included in the 65 RCT's that provided the quantitative data for this review. (See Tables 2 and 3 and *Supplementary Appendix Table 1* for individual study details) None of the studies included were of a low risk of bias in every domain. A summary of the risk of bias analysis is presented in the *Supplementary Appendix*.

Results

Mortality

The primary outcome of interest was mortality at one year. However, only one trial reported mortality at one year,(20) (in which the mortality in both oral iron and no iron group was 29% (p=1)) therefore hazard ratio was not calculated for any of the comparisons.

Eight studies investigated oral iron vs. inactive control and reported mortality, (20, 23, 60-64, 66) 19 studies compared parenteral iron vs. inactive control (27, 29, 31-33, 35-40, 45, 46, 60-64, 66) and 13 trials reported mortality comparing parenteral iron vs. oral iron.(47, 48, 51, 53-55, 57, 60-64, 66) (*Figures 2-4)* In all comparisons there was no statistically significant difference in mortality. (*Table 4)*

Proportion requiring blood transfusion

Comparing oral iron vs. inactive control,(19, 21, 62, 64, 66) there was a lower transfusion rate in the oral iron group (RR 0.66 (95% CI 0.48 to 0.90)). (Supplementary Appendix *Figure 1)* When comparing parenteral iron vs. inactive control statistically significant differences in participants who received blood transfusion were shown (RR 0.84, 95% CI 0.73 to 0.97). (27, 29-35, 38, 43, 45, 46, 62, 64, 66) (Supplementary Appendix *Figure 2)* In those studies that reported mean blood transfused, this was significantly lower in the parenteral iron group than the inactive control group (MD -1.71 units; 95% CI -3.20 to -0.22). (29, 32, 34, 48) No statistically significant difference between the two groups was found comparing parenteral to oral iron. (47, 48, 62, 64, 66)(*Figure 5)* (*Table 4)*

Haemoglobin

Oral iron resulted in higher haemoglobin levels compared to inactive controls (MD 0.91 g/dL (95% CI 0.48 to 1.35); I^2=67%; chi^2 test for heterogeneity P=0.0004). (20, 22-26, 60-65) There was significant heterogeneity (I^2=67%), with a point estimate of the mean difference in haemoglobin levels ranging from 0.2 g/dL to 2.2 g/dL higher in the oral iron group than in the inactive control group. (*Supplementary Appendix figure 3)* Parenteral iron resulted in higher haemoglobin levels than inactive controls (MD 1.04 (95% CI 0.52to1.57); I^2=93%; Chi^2 test for heterogeneity P<0.00001)). (27, 30- 33, 35, 36, 38-48, 50, 60, 61, 63-66, 68-70) (*Supplementary Appendix figure 4)* Again there was considerable heterogeneity (I^2=93%), with a point estimate of the mean difference in haemoglobin levels ranging from -0.7 g/dL to 3 g/dL higher in the parenteral iron group than in the inactive control group. Comparing parenteral vs. oral iron, haemoglobin concentration was higher in the parenteral iron group (MD 0.53 (95% CI 0.31 to 0.75). (47, 48, 50-58, 60-65)(*Figure 6*)

Quality of life

Six trials reported quality of life when comparing parenteral iron to inactive control (27, 29, 39, 40, 46, 66) using a variety of scales. Quality of life was higher in the parenteral iron group than the control group SMD 0.22 ((95% CI -0.00 to 0.45); I^2= 74%; chi^2 test for heterogeneity P=0.002). (*Figure 7*) When comparing parenteral and oral iron, there was no significant difference in quality of life (SMD 0.01 (95% CI -0.09 to 0.12)). (47, 48, 51, 55-57, 66)(*Figure 8*)

Serious adverse events

In comparisons of oral iron vs. inactive control, (20, 23-25, 60, 62, 64, 66) and parenteral iron vs. inactive control, (27, 31, 32, 34, 37, 40, 46, 60, 62, 64, 66) there were no statistically significant differences found. (*Supplementary Appendix figure 5 and 6)* Importantly, no trials reported severe allergic reactions from parenteral iron. There was no statistically significant difference in serious adverse events when comparing parenteral to oral iron. (47, 48, 50-55, 57, 58, 60, 62, 64, 66) (*Figure 9) (Table 4)*

Length of hospital stay

One study compared length of hospital stay for oral iron vs. inactive control,(20) whilst one trial compared length of hospital stay for parenteral versus oral iron;(47) neither showed any significant difference.

Subgroup Analysis – Chronic Heart Failure

Only one study included comparison of oral to parenteral iron, and oral iron to inactive control in heart failure, reporting mortality and haemoglobin concentration.(63) Subgroup analysis of oral to parenteral iron in patients with heart failure versus those without revealed no significant subgroup differences in mortality (p=0.44) or haemoglobin (p=0.59). When comparing oral iron to inactive control in patients with and without heart failure there was no significant difference in mortality (p=0.39) and haemoglobin concentration (p=0.93) between the groups.

Comparing parenteral iron to inactive control in patients with and without heart failure showed no significant difference in mortality (p=0.79), haemoglobin

(p=0.99), quality of life (p=0.95) or serious adverse events (p=0.14) between these groups.

In patients with heart failure the point estimate haemoglobin concentration was significantly higher in patients given intravenous iron compared to placebo (MD 1.12 (95%CI 0.11 to 2.14), yet without any significant difference in mortality, quality of life or serious adverse events.

Heterogeneity

The heterogeneity within the studies ranged from low (for mortality, I^2=0, and serious adverse events, to considerable for haemoglobin (I^2=67% for oral iron vs. inactive control, I^2=93% for parenteral iron vs. inactive control and I^2=41% for parenteral vs. oral iron.

Discussion

This systematic review reviewed the utility of iron therapy for the treatment of anaemia in non-peripartum anaemic adults without chronic kidney disease. Most of the trials included patients with mild to moderate anaemia. The trials did not demonstrate clinical benefit in terms of mortality. In all comparisons there were no significant subgroup differences in the results comparing patients with and without heart failure.

Both oral and parenteral iron led to higher level of haemoglobin compared to inactive controls, and parenteral iron demonstrated a statistically significant rise in comparison to oral iron.

Parenteral iron demonstrated a statistically significant benefit in quality of life when compared to inactive control but no significant difference when compared to oral iron. It was not possible to estimate the clinical importance of this difference. The only trial comparing oral iron to inactive control showed no statistically significant difference.(66)

Both oral iron and parenteral iron demonstrated a significant reduction in the risk of blood transfusion when compared to inactive control, with no significant difference between the two modes of administration when compared to one another.

There was no significant difference in the proportion of patients who developed serious adverse events as a result of parenteral or oral iron therapy. Most trials reporting serious adverse events reported that there were no allergic or anaphylactic reactions or serious reactions, suggesting that these are rare.

Parenteral iron was demonstrated to result in increased haemoglobin levels and a reduction in blood transfusion when compared to inactive controls, without any statistically significant increase in adverse events. However, no improvement in quality of life or mortality was demonstrated in these studies.

Most of the adverse events related to oral iron therapy were gastrointestinal side effects such as nausea, diarrhoea or constipation. While the balance of the benefits and harms of oral iron therapy appear to favour routine oral iron therapy in anaemic patients, the quality of evidence is very low. There were no significant clinical benefits of one iron preparation or regimen over another.

Thus, there is little evidence on to recommend one preparation or regimen over another.

Subgroup analyses were performed to determine whether iron would be useful in specific clinical situations or whether iron therapy might be useful in patients who are receiving erythropoietin. The results were not consistent enough to enable us determine this. In anaemic patients with heart failure, iron improved the haemoglobin concentration without any improvement in other clinically relevant endpoints.

This analysis is applicable only in non-peripartum anaemic adults without chronic kidney disease with mild to moderate anaemia. It should also be noted that most trials excluded patients who were allergic to iron therapy and measured the ferritin and transferrin levels to ensure that the patients had iron deficiency anaemia.

None of the trials were of a low risk of bias in every domain assessed. Many trials did not report important clinical outcomes, although it is likely that such clinical outcomes were measured. This has resulted in significant selective outcome reporting bias. We did found evidence of publication bias in haemoglobin levels and we found evidence of selective reporting, i.e. many clinical trials reported haemoglobin levels but not clinical outcomes. We imputed the mean and standard deviation when these were not available. This could have introduced bias. However, there was no evidence of such a bias when exclusion of trials with imputed data did not alter the results significantly.

The previous systematic review of iron in non-pregnant and non-lactating anaemic adults without chronic kidney disease failed to show any clinical benefit of intravenous iron compared to oral iron or inactive controls beyond improving haemoglobin levels.(11) This expanded meta-analysis showed a statistical difference in blood transfusion rates and quality of life for parenteral iron when compared to inactive control. However, the clinical significance of this is not known, particularly since there was no difference in mortality rates. There is a growing recognition that anaemia is a significant comorbidity in patients that may not be modifiable, whether by iron replacement, or blood transfusion. In heart failure, treatment of iron deficiency itself may be more important than anaemia per se.

The recognition of functional iron deficiency modulated by hepcidin, and its associate with inflammation provides an explanation for the efficacy of parenteral iron when compared to oral iron in producing a rise in haemoglobin in anaemic patients. In spite of demonstrating a greater haemoglobin response than oral iron, parenteral iron failed to show any other benefits over oral preparations.

In the context of heart failure with or without anaemia, intravenous iron has been shown to reduce readmission to hospital,(84) and to improve renal function.(85) Iron replacement is recommended for all iron deficient patients with heart failure, regardless of whether they are anaemic. The majority of patients with heart failure receive oral iron, despite evidence lacking for its benefit in these patients.(86) Only one trial comparing oral versus intravenous iron in anaemic patient with heart failure was included in this systematic

review,(63) and further trials are required comparing oral to intravenous iron in anaemic patients with heart failure.

Recently, a systematic review was published which included all trials in which intravenous iron was compared with either oral iron or no iron therapy irrespective of the clinical setting.(87) Our findings are broadly similar to that review which found that intravenous iron increased haemoglobin levels and decreased transfusion requirements. However, that systematic review found infective complications higher with intravenous iron. In this review, there were no significant differences in the serious adverse events. However, the confidence intervals were wide and so the observation is our systematic review might have been due to lack of evidence of effect rather than lack of effect.

In conclusion, intravenous iron is effective in improving haemoglobin levels compared to oral iron or inactive controls. Oral iron improves haemoglobin levels in comparison to inactive control. Neither reduced mortality, however both reduced blood transfusion rates, and parenteral iron demonstrated statistically significant improvement in quality of life, although the clinical significance of this increase is not known. The analysis of trials of heart failure patients within this study showed the same outcomes. From these findings, more randomised controlled trials at a low risk of bias, powered to measure clinically useful endpoints including mortality, blood transfusion and quality of life are still required in all patient populations, including those with heart failure.

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Conflict of interest

BC is currently the clinical research associate for PREVENTT (preoperative intravenous iron to treat anaemia in major surgery), a multicentre trial funded by a National Institute for Health Research Health Technology Assessment (NIHR HTA) grant.

KG has no conflicts of interest.

AK has received an educational grant, honoraria and travel expenses from Pharmacosmos, who manufacture a formulation of intravenous iron.

GJM has no conflicts of interest.

SDA has received consultancy fees, educational grants and travel expenses from Vifor International, who manufacture a formulation of intravenous iron.

TR is currently chief investigator for the PREVENTT trial. UCL and the research program lead by TR has received research funding from a variety of sources including; government, charity and industry sources for research into anaemia, blood transfusion and iron therapy including: NIHR HTA, Health Foundation, Gideon Richter, Covidien, Vifor Pharma Ltd, Pharmacosmos. TR has also been an invited speaker at conferences on anaemia, blood transfusion and iron therapy in the last 5 years.

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Figure Legends

Table 1: Inclusion and exclusion criteria

WHO – World Health Organisation; Hb – haemoglobin

Table 2: Characteristics of included studies

Table 3: Clinical setting of included studies

Table 4: Summary of results

RR – Risk Ratio; CI – Confidence Interval; MD – Mean Difference; SMD – Standardised Mean Difference; SE – Standard Error

***** Denotes statistical significance

Figure 1: Study selection flow diagram

Figure 2: Oral iron vs inactive control - Mortality

Forest plot of risk ratios (RRs) with 95% confidence intervals (CIs) comparing oral iron with inactive control for mortality.

Squares indicate study-specific RR estimates; horizontal lines indicate the 95% CI; diamonds indicate the pooled RRs with their 95% CI.

Figure 3: Parenteral Iron vs Inactive Control: Mortality

Forest plot of risk ratios (RRs) with 95% confidence intervals (CIs) comparing parenteral iron with inactive control for mortality.

Squares indicate study-specific RR estimates; horizontal lines indicate the 95% CI; diamonds indicate the pooled RRs with their 95% CI.

Figure 4: Parenteral vs Oral Iron: Mortality

Forest plot of risk ratios (RRs) with 95% confidence intervals (CIs) comparing parenteral with oral iron for mortality.

Squares indicate study-specific RR estimates; horizontal lines indicate the 95% CI; diamonds indicate the pooled RRs with their 95% CI.

Figure 5: Parenteral vs Oral Iron: Proportion requiring blood transfusion

Forest plot of risk ratios (RRs) with 95% confidence intervals (CIs) comparing parenteral with oral iron for blood transfusion.

Squares indicate study-specific RR estimates; horizontal lines indicate the 95% CI; diamonds indicate the pooled RRs with their 95% CI.

Figure 6: Parenteral vs Oral Iron: Haemoglobin

Forest plot of mean differences (MDs) with 95% confidence intervals (CIs) comparing parenteral with oral iron for haemoglobin concentration.

Squares indicate study-specific MD estimates; horizontal lines indicate the 95% CI; diamonds indicate the pooled RRs with their 95% CI.

Figure 7: Parenteral Iron vs Inactive Control: Quality of Life

Forest plot of standardised mean differences (SMDs) with 95% confidence intervals (CIs) comparing parenteral iron with inactive control for effect upon quality of life.

Squares indicate study-specific SMD estimates; horizontal lines indicate the 95% CI; diamonds indicate the pooled RRs with their 95% CI.

Figure 8: Parenteral vs Oral Iron: Quality of Life

Forest plot of standardised mean differences (SMDs) with 95% confidence intervals (CIs) comparing parenteral with oral iron for effect upon quality of life.

Squares indicate study-specific SMD estimates; horizontal lines indicate the 95% CI; diamonds indicate the pooled RRs with their 95% CI.

Figure 9: Parenteral vs Oral Iron: Serious adverse events

Forest plot of risk ratios (RRs) with 95% confidence intervals (CIs) of serious adverse events comparing parenteral iron with inactive control.

Squares indicate study-specific RR estimates; horizontal lines indicate the 95% CI; diamonds indicate the pooled RRs with their 95% CI.