

BMJ Open Risk of infection associated with intravenous iron preparations: protocol for updating a systematic review

Akshay Shah,¹ Anita Sugavanam,² Jack Reid,² Antony J Palmer,³ Edward Dickson,⁴ Susan Brunskill,⁵ Carolyn Doree,⁶ Charles M Oliver,⁷ Austin Acheson,⁸ Ravi Rao Baikady,⁹ Sohail Bampoe,¹⁰ Edward Litton,¹¹ Simon Stanworth¹²

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For numbered affiliations see end of article.

Correspondence to

Dr Akshay Shah;
akshay.shah@ndcls.ox.ac.uk

ABSTRACT

Introduction The benefits and risk of intravenous iron have been documented in previous systematic reviews and continue to be the subject of randomised controlled trials (RCTs). An ongoing issue that continues to be raised is the relationship between administering iron and developing infection. This is supported by biological plausibility from animal models. We propose an update of a previously published systematic review and meta-analysis with the primary focus being infection.

Methods and analysis We will include RCTs and non-randomised studies (NRS) in this review update. We will search the relevant electronic databases. Two reviewers will independently extract data. Risk of bias for RCTs and NRS will be assessed using the relevant tools recommended by The Cochrane Collaboration. Data extracted from RCTs and NRS will be analysed and reported separately. Pooled data from RCTs will be analysed using a random effects model. We will also conduct subgroup analyses to identify any patient populations that may be at increased risk of developing infection. We will provide a narrative synthesis on the definitions, sources and responsible pathogens for infection in the included studies. Overall quality of evidence on the safety outcomes of mortality and infection will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation approach.

Ethics and dissemination This systematic review will only investigate published studies and therefore ethical approval is not required. The results will be broadly distributed through conference presentations and peer-reviewed publications.

Trial registration number PROSPERO (CRD42018096023).

INTRODUCTION

Treating anaemia is a key pillar of patient blood management and a recent James Lind prioritisation exercise ranked the timely identification of anaemia and treatment as a top 10 priority for research into blood transfusion and blood donation.¹ Systematic reviews have shown the efficacy of intravenous iron with regards to treating anaemia and reducing

Strengths and limitations of this study

- Systematic review protocol primarily focusing on a safety outcome (risk of infection) with intravenous preparations.
- Comprehensive review that will include data from randomised controlled trials and non-randomised studies.
- Infection is not often a predefined endpoint in published studies and definitions of infection will vary across studies.
- There will be considerable heterogeneity in participant populations, doses and types of intravenous iron used and follow-up time points.

blood transfusion requirements,^{2 3} although with varying degrees of effect size and the primary outcomes in majority of trials were haematological (change in haemoglobin concentration, transfusion requirements) instead of clinical outcomes (eg, quality of life).

Despite the widespread use of intravenous iron,^{1 2} uncertainty persists as to whether intravenous iron is associated with an increased risk of infection. The uncertain relationship between iron and infection has long been postulated and remains a topic of interest in ongoing trials of oral iron, for example, in the setting of malaria and other tropical infections in low-resource country settings.⁴ Iron is essential for extracellular pathogens as it is an ideal redox catalyst for important cellular processes such as respiration and DNA replication.⁵ Humans are able to withhold free (non-transferrin-bound) iron from invading pathogens through a process termed nutritional immunity in an effort to limit infection.^{5 6} Intravenous iron administration can lead to increased levels of circulating free iron, which can be detrimental to the host and promote pathogen growth. Such

an interaction is supported by biological plausibility in recent animal models where the administration of intravenous iron worsening shock, lung injury and mortality.⁷

Two recent systematic reviews have investigated the efficacy and safety of intravenous iron therapy.^{2,7} The first systematic review identified 72 randomised controlled trials (RCTs) that included 10 605 participants. The authors reported a reduced risk of requirement for red blood cell (RBC) transfusion (risk ratio (RR) 0.74, 95% CI 0.62 to 0.88; 22 RCTs, 3321 participants). Of note, this potential benefit was counterbalanced a significantly increased risk of infection (RR 1.34, 95% CI 1.10 to 1.64; 24 RCTs, 4400 participants) when intravenous iron was compared with oral iron or no iron.² The second systematic review pooled data from 32 RCTs and showed a point estimate which again favoured infection, although this was statistically non-significant (RR 1.17; 95% CI 0.83 to 1.65).⁸ Interpreting data on infection from these meta-analyses is challenging because infection is not always defined as a prespecified, standardised outcome measure in RCTs but rather reported as safety outcome. A recent editorial highlighted the need for an adequately powered trial of intravenous iron with infection as a primary outcome.⁶

Given the ongoing uncertainty regarding the risk of infection, the primary objective of this systematic review was to update the previous review by Litton *et al*³ by identifying and incorporating recent trial data to evaluate the safety data for intravenous iron on the risk of infection across all clinical settings. A better understanding of the characterisation of infection in patients receiving iron therapy will help inform the design of subsequent trials in particular groups of patients (eg, critically ill, emergency surgery) in whom the risk of infection is of clinical concern. Our secondary objective is to continue to collect efficacy data to focusing primarily on changes in haemoglobin concentration, transfusion requirements and functional outcomes.

METHODS

We used the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols reporting guidelines.⁹ Studies will be selected according to the criteria outlined below.

Eligibility criteria

We will include RCTs from 1 January 2013 onwards as the last search date for the previous review was June 2013.² We will also include non-randomised studies (NRS) in this updated review as infection may not always be reported in RCTs and the findings of infection outcomes reported in NRS may be useful to inform the design of a future RCT. We will only include NRS that meet the following criteria:

- ▶ Published since 1 January 2007 as this is the year from which newer intravenous iron preparations (Ferinject, Monofer, Venofer, Injectofer) received and/or renewed their marketing authorisation. Therefore,

any data extracted is likely to be reflective of current practice. Studies evaluating low molecular weight dextran (INFed, Cosmofer), ferumoxytol, ferric pyrophosphate citrate (TriFerac) and iron polymaltose will also be included.

- ▶ At least two comparable groups (including controlled before and after, and prospective/retrospective cohort studies).
- ▶ Quasi-RCTs.
- ▶ Provide data on our primary outcome of infection.

We will exclude any studies that provide no outcome data of interest, NRS published before 1 January 2007 and NRS that do not have an intravenous iron comparison arm. We will include studies examining all participant populations (including paediatrics, pregnancy) but excluding healthy volunteers. Included studies would compare intravenous iron to no iron/placebo or oral iron.

Our primary outcome of interest is the number of patients who develop an infection as defined by the study authors. Secondary safety and efficacy outcomes include:

- ▶ Mortality—short-term (≤ 30 days), long-term (> 30 days).
- ▶ Hospital length of stay.
- ▶ Change in haemoglobin concentration from baseline/pre-treatment levels to end of study period.
- ▶ Transfusion requirements during study period (% transfused, mean number of RBC units transfused).

Information sources and search strategy

We will search the following databases for RCTs (from 1 January 2013), systematic reviews and NRS (from 1 January 2007)—Cochrane Central Register for Controlled Trials; Medline (Ovid interface); Ovid Interface; Cumulative Index to Nursing and Allied Health Literature (CINAHL); Transfusion Evidence Library; Web of Science Conference Proceedings Citation Index Science. This will be supplemented by searching ongoing trial databases such as ClinicalTrials.gov and WHO International Clinical Trials Search Registry Platform. Citation lists of included studies and relevant reviews will also be scanned to identify any studies missed by the search. A draft Medline search strategy is included in online supplementary appendix 1.

Study selection

Literature search results will be uploaded to Covidence, a web-based software platform, to facilitate citation screening between reviewers. Review authors will independently screen the titles and abstracts yielded by the search against the prespecified inclusion criteria. Two review authors will then independently screen the full-text reports and decide whether these meet the inclusion criteria. Disagreements will be resolved through discussion, and if necessary, referred to a third reviewer. The study selection process will be reported in a PRISMA flow diagram.

Data extraction

For RCTs, two reviewers will use the data extraction form used for the original review to extract data independently. We will standardise and pilot a data extraction form for NRS and items for extraction from NRS will include:

- ▶ Data on confounding factors.
- ▶ Comparability of groups based on the consideration of confounding factors.
- ▶ Methods used to control for confounding.
- ▶ Effect estimates—both adjusted and unadjusted if available.

For both sets of studies, we will extract the following additional data, if reported, on the outcome of infection:

- ▶ Definition of infection used (ie, guideline based, laboratory based, clinical discretion).
- ▶ Site of infection (eg, lung, wound, gastrointestinal).
- ▶ Reporting of identified pathogens.
- ▶ Antibiotic usage.

Disagreements will be resolved through discussion, and if necessary, referred to a third reviewer. We will contact study authors to resolve any uncertainties.

Risk-of-bias assessment

Risk of bias for the RCTs will be reported using the Cochrane Risk of Bias tool.¹⁰ For the non-RCT data, risk of bias will be reported using the Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) developed by the Cochrane Bias Methods Group.¹¹ Two reviewers will make these judgements independently.

Data synthesis

Data from RCTs and NRS will be analysed and reported separately.

RCTs

The primary endpoint will be the proportion of participants who developed an infection. Dichotomous outcomes (infection, mortality, requirement for blood transfusion) will be reported as RRs with corresponding 95% CIs. Continuous outcomes will be reported as weighted mean (with 95% CI) or standardised mean differences (95% CI) as appropriate. For continuous measures, the mean difference in change from baseline values between groups will be used preferentially; if change from baseline values is not reported, then the mean difference in measures at follow-up will be used. The unit of analysis will be per individual randomised. Data from included studies will be pooled for meta-analysis using a random effects model. Statistical heterogeneity will be tested using the I^2 statistic and $I^2 > 50\%$ will be considered as substantial heterogeneity. If substantial heterogeneity is present among the trials, the study characteristics of the included studies will be analysed and we will attempt to explain the heterogeneity by subgroup analysis or sensitivity analysis. If sufficient data are available, we will undertake metaregression to examine the effect of cumulative intravenous iron dose and the incidence of infection in the control group (as a surrogate for background/endemic burden

of infection) on our primary outcome. Statistical analysis will be conducted on RevMan V.5.1. and STATA (V.14, StataCorp LP, College Station, Texas, USA).

NRS

For NRS, we will only report results descriptively on the primary outcome of infection instead of pooling results due to heterogeneity in clinical conditions, study designs and variations in statistical adjustment. If possible, results will be displayed in a forest plot, with studies sorted according to study design features, and the pooled estimate will be suppressed as recommended by the Cochrane Collaboration.⁶

Analysis of subgroups

Subgroup analysis of the primary safety outcome (infection) will be performed on the following:

- ▶ Clinical settings (in-patient medical (any), outpatient (any), elective surgical, non-elective (urgent/emergency) surgical, obstetrics, paediatrics, critically ill).
- ▶ Different iron profiles at enrolment as defined by the study authors (true iron deficiency, functional iron deficiency, iron-restricted erythropoiesis).
- ▶ Mode of administration (eg, single dose, continuous infusion, multiple boluses).
- ▶ Cumulative dose of intravenous iron.
- ▶ Incidence of infection in the control group.

We will carry out a sensitivity analysis on infection and mortality outcomes by excluding studies with a high risk of bias. We will assess for publication bias on the primary outcome with a funnel plot if ≥ 10 studies are available, plotting the OR for proportion that develop infection against the SE of the log OR.

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise data on infection provided in the include studies. This narrative synthesis will explore the definitions of infection used, reporting of infection source and pathogens and antibiotic use.

Confidence in cumulative evidence

According to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, we will assess the overall quality of evidence for the main safety outcomes of infection and mortality.¹² In line with current GRADE guidance, if the certainty of evidence differs between RCTs and NRS, we will present summary of findings tables for the higher certainty of evidence. If the certainty ratings are the same, results from both bodies will be presented separately.¹³

Patient and public involvement

Patients and members of the public were not directly involved in the design of this study. However, appropriate management of anaemia, through interventions such as iron therapy, has been identified as a key research priority in a recent James Lind Priority Setting Partnership exercise.¹

DISCUSSION

Recent patient blood management efforts have attempted to reduce blood transfusion by using alternative therapies such as intravenous iron. Safety concerns surrounding older preparations, mainly anaphylaxis, have been allayed by the development of newer, stable preparations which has led to intravenous iron being used more frequently in multiple settings.¹⁴ Despite its widespread use, concerns surrounding infection remain both from systematic reviews and animal models.

Our review will provide an up to date and comprehensive estimate of the risk of infection associated with intravenous iron preparations across multiple patient groups. In addition, we will also provide data on the characterisation of infection as a step towards standardising infection as an outcome measure for future trials of intravenous iron.

Author affiliations

¹Radcliffe Department of Medicine, University of Oxford, Oxford, UK

²Department of Anaesthetics, Brighton and Sussex University Hospitals NHS Trust, Brighton and Hove, UK

³Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

⁴Department of Colorectal Surgery, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

⁵Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK

⁶NHS Blood and Transplant, John Radcliffe Hospital, Oxford, UK

⁷Division of Biosciences, University College London, London, UK

⁸Department of Colorectal Surgery and NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases, Queen's Medical Centre, Nottingham, UK

⁹Department of Anaesthetics, Perioperative Medicine and Pain, Royal Marsden NHS Foundation Trust, London, UK

¹⁰Department of Anaesthesia and Perioperative Medicine, University College London Hospitals NHS Foundation Trust, London, UK

¹¹Intensive Care Unit, St John of God Hospital, Perth, Western Australia, Australia

¹²Department of Haematology/Transfusion Medicine, Oxford Radcliffe Hospitals Trust, Oxford, UK

Contributors AS, AS, SS and EL conceived the idea for the review update. AS prepared the initial protocol draft with input from SB and SS who contributed to the revision of the manuscript. CD will perform the search and AS, JR, AJP and ED will screen and extract data. All listed authors, including CMO, AA, RRB and SB, contributed to the development of the idea and drafting and revisions of the manuscript.

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REFERENCES

- Hibbs SP, Brunskill SJ, Donald GC, *et al*. Setting priorities for research in blood donation and transfusion: outcome of the James Lind Alliance priority-setting partnership. *Transfusion* 2019;59.
- Clevenger B, Gurusamy K, Klein AA, *et al*. Systematic review and meta-analysis of iron therapy in anaemic adults without chronic kidney disease: updated and abridged Cochrane review. *Eur J Heart Fail* 2016;18:774–85.
- Litton E, Xiao J, Ho KM, Km H. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. *BMJ* 2013;347:f4822.
- Pasricha SR, Armitage AE, Prentice AM, *et al*. Reducing anaemia in low income countries: control of infection is essential. *BMJ* 2018;362:k3165.
- Cassat JE, Skaar EP. Iron in infection and immunity. *Cell Host Microbe* 2013;13:509–19.
- Youssef LA, Spitalnik SL. Iron: a double-edged sword. *Transfusion* 2017;57:2293–7.
- Suffredini DA, Xu W, Sun J, *et al*. Parenteral irons versus transfused red blood cells for treatment of anemia during canine experimental bacterial pneumonia. *Transfusion* 2017;57:2338–47.
- Avni T, Bieber A, Grossman A, *et al*. The safety of intravenous iron preparations: systematic review and meta-analysis. *Mayo Clin Proc* 2015;90:12–23.
- Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- Higgins JP, Altman DG, Gotzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
- Atkins D, Best D, Briss PA, *et al*. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
- Schünemann HJ, Cuello C, Akl EA, *et al*. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol* 2018.
- Auerbach M, Macdougall IC. Safety of intravenous iron formulations: facts and folklore. *Blood Transfus* 2014;12:296–300.