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Intravenous iron therapy for non-anaemic iron deficient adults (Protocol)

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[Intervention Protocol]

Intravenous iron therapy for non-anaemic iron deficient adults

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of intravenous iron supplementation in the treatment of non-anaemic iron deficiency in adult patients.

BACKGROUND

Description of the condition

Elemental iron is ubiquitous in the biosphere and has been incorporated into the essential physiological processes of many organisms, including humans (Abbaspour 2014). Depletion of bodily iron stores has a number of manifestations, with profound physiological consequences. The most recognised complication of iron deficiency is anaemia, as the lack of iron results in failure of haemoglobin production (WHO 2001). However, anaemia is effectively the final stage of iron deficiency, and early forms of the disease can be of detriment to physical health and well-being, with fatigue, diminished mental acuity, reductions in work capacity and productivity, and reduced exercise tolerance all being reported in the literature.

The identification and management of iron deficiency (particularly early, or non-anaemic iron deficiency) is made challenging by different forms of the disease. Broadly speaking, iron deficiency takes the following two forms (Goodnough 2012):

1. Absolute iron deficiency: this refers to the absence of sufficient iron stores to maintain effective erythropoiesis (Goodnough 2011; Pasricha 2013). This is normally due to increased requirements in excess of stored iron, decreased intake of dietary iron, increased red cell loss or decreased absorption of dietary iron (Nelson 1994; Reveiz 2011). The condition is not associated with a derangement in iron regulatory or erythropoietic mechanisms.
2. Functional iron deficiency: this exists where, despite an apparently adequate store, iron cannot be effectively mobilised to participate in erythropoiesis (Pasricha 2010). Understanding the pathophysiology of functional iron deficiency was greatly enhanced by the discovery of the 25-amino acid peptide, hepcidin (Beard 2001; Drakesmith 2012; Ganz 2003; Goodnough 2011; Jordan 2009; Krause 2000; Nemeth 2004; Nemeth 2004a; Park 2001; Weiss 2005).

In a healthy patient, simple indices of iron status such as ferritin (a storage form of iron predominately found in the liver which is detectable in serum as it leaks into the circulation) and transferrin saturation (percentage occupation of iron carrier molecules in the circulation) are sufficient to diagnose iron deficiency (Lim 2018).

However, in the setting of inflammation, ferritin acts as an acute phase reactant and serum concentration increases, meaning interpretation of ferritin alone as a measure of iron deficiency becomes unreliable. Simultaneously, in response to the same inflammatory process that makes serum ferritin difficult to interpret, a 25-amino acid protein is produced, known as hepcidin. The functions of hepcidin are two-fold:

1. prevention of iron overload through limiting excessive iron absorption in the proximal small intestine and regulation of iron release from macrophages participating in recycling (Ganz 2003), and;
2. prevention of iron acquisition by pathogens as a component of innate immunity (Krause 2000).

Hepcidin impairs the function of the key iron regulatory protein, ferroportin, thereby preventing the transport of iron across basement membranes (Nemeth 2004). This inhibits the uptake of iron from the gastrointestinal tract, the transport of stored iron out of the liver, and the reclamation of iron from circulating macrophages. Whilst serum levels of ferritin appear high, iron is unable to circulate or be delivered to the bone marrow, which in turn leads to iron-restricted erythropoiesis (Weiss 2005).

Description of the intervention

In this systematic review, we will investigate intravenous iron supplementation as the intervention. Current guidelines recommend oral iron as the first line of treatment for iron deficient patients. However, oral iron supplementation is associated with multiple issues relating to compliance and efficacy.

1. Oral iron may result in gastrointestinal side effects, meaning that adherence to therapy may be poor (Cancelo-Hidalgo 2013; Gereklioglu 2016).
2. Use of oral supplementation does not lead to rapid incorporation of iron into the body. This is especially true in functional iron deficiency, where inflammation prevents the transport of iron across the enterocyte due to the activity of the hepcidin-ferroportin axis (Goodnough 2012; Nemeth 2004; Nemeth 2004a; Nemeth 2009).
3. Correction of haemoglobin levels using oral supplementation alone may be slow, sometimes requiring weeks of therapy until substantive gains are made, and gains may be attenuated by ongoing blood loss (Cançado 2011; Johnson-Wimbley 2011).

These issues are avoided by giving iron through the intravenous route. By bypassing the hepcidin-ferroportin axis, the treatment has a higher degree of clinical effect in the setting of inflammation, and does not have the same gastrointestinal side effects of oral iron. Consequently, intravenous iron preparations are being used more widely for patients who, under previous guidelines, would not have received this therapy as first-line treatment (Favrat 2014). Previously, parenteral iron preparations were highly labile and prone to the excessive release of free iron into the circulation, with an associated risk of side effects (Bailie 2012). However, the development of newer, high-molecular-weight, stable preparations has markedly reduced the incidence of these events (Avni 2015; Muñoz 2017), and consequently, administration of parenteral iron is becoming more widespread.

How the intervention might work

Iron supplementation has been increasingly advocated in a variety of clinical scenarios including perioperative optimisation of haemoglobin (Clevenger 2015). Iron is a limiting factor to oxygen transport and storage when iron is insufficient for erythropoiesis (Ganz 2012). Iron deficiency may also affect adenosine triphosphate (ATP) production and increase the predominance of energy production towards anaerobic sources, such as anaerobic glycolysis (Hinton 2014; Melenovsky 2016).

Accordingly, even in the absence of anaemia, insufficient iron stores may have non-haematological effects that are detrimental to health, well-being and functional status. This hypothesis has been tested in people with heart failure, where insufficient iron stores are associated with impaired exercise performance, increased fatigue and reduced health-related quality of life (Jankowska 2016; Klip 2013), and administration of iron supplementation may address these symptoms (Burden 2015).

As noted previously, oral iron supplementation for the treatment of iron deficiency has several limitations related to efficacy and compliance. The use of intravenous iron in scenarios where a rapid response is required, or where inflammation is present, is considered preferable. It has been hypothesised that the administration of large amounts of intravenous iron, and subsequent overload of the reticuloendothelial capacity for iron, leads to a transient and compensatory reduction in hepcidin expression, allowing replenishment of iron stores through export from the plasma (Cançado 2011).

Why it is important to do this review

It has been recognised for some time that iron deficiency is a staged process, and that anaemia, whilst the most recognisable manifestation of this pathology, effectively represents the end stage of the disease (Suominen 1998). Observational studies from different populations have highlighted the impact of the pathology on exercise performance and fatigue (Barberan-Garcia 2015; Pratt 2016), as well as the benefits of correction (Favrat 2014). Recently, a number of peri-operative guidelines and consensus statements have advocated for the correction of iron deficiency in patients about to undergo major surgery (National Blood Authority 2012; Muñoz 2017).

Pathological organisms also rely on iron for key functions. It is increasingly recognised that certain regulatory processes in the body exist to reduce the availability of free iron in the circula-

tion at times of inflammation and infection (Drakesmith 2012; Ganz 2003; Nemeth 2009). It has been postulated that administration of parenteral iron to bypass these regulatory mechanisms may lead to an increased risk of bacterial infection (Drakesmith 2012). Evidence for this effect is conflicting: a systematic review in hospital inpatients found a 33% increased risk of infection where parenteral iron was administered (Litton 2013), but this is not reflected in large, retrospective cohort analyses (Muñoz 2014), or other meta-analyses examining the safety of newer, high-molecular-weight iron preparations (Avni 2015; Rognoni 2016). Evidence from developing countries suggests that population-based interventions to address the high incidence of nutritional iron deficiency concomitantly increased the incidence of infectious diseases (Pasricha 2013).

Given these apparent conflicts, there is a need for further clarification of the role of iron therapy to treat non-anaemic iron deficiency. There are several reasons to assess the effects of intravenous iron on the correction of non-anaemic iron deficiency across patient groups:

1. the current definition of anaemia in the non-pregnant adult is not dependent on the presence or absence of comorbidities and is based on historical expert consensus (Butcher 2017);
2. a haemoglobin concentration above the historical threshold for anaemia may still be clinically important, particularly for women (Favrat 2014);
3. intravenous iron therapy for patients with anaemia is associated with an increase in haemoglobin in a wide variety of clinical scenarios;
4. in patients undergoing major surgery, a higher haemoglobin at the start of operation has been shown to be the only correctable factor protecting against allogeneic blood transfusion (Klein 2017);
5. iron depletion may have pronounced metabolic effects, even in the absence of anaemia, particularly with respect to fatigue and cognition (Favrat 2014); and
6. iron depletion (even in the absence of anaemia) worsens the functional capacity (and the effect of corrective interventions) of a variety of different patient populations (Barberan-Garcia 2015; Pratt 2016).

There is yet to be a systematic review determining the aggregate effect of intravenous iron supplementation on features of iron deficiency other than anaemia. Such a review has the potential to substantially guide practice in this evolving area, where intravenous iron supplementation is increasingly being used for the management of non-anaemic iron deficiency. A high-quality summary of the evidence is required to adequately inform practice, and direct the development of future randomised controlled trials.

OBJECTIVES

To assess the effects of intravenous iron supplementation in the treatment of non-anaemic iron deficiency in adult patients.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomised controlled trials (RCTs) for inclusion in this review. We will include RCTs irrespective of blinding, language of publication, publication status, date of publication, study setting or sample size. We will not include quasi-randomised trials, cluster-randomised trials or other non-RCT designs. Examples of quasi-randomised trials are any controlled trials where the method of allocation is not truly random (i.e. allocation based on medical record number, date of birth, day of week, etc.). Cluster-randomised trials will be included provided that the method of randomisation is truly random (i.e. random number sequence, coin flip, etc.). We will exclude cross-over trials as this is not an appropriate design to assess this intervention. Trials that were not prospectively registered and were published after 2010 will not be included in the analysis, although similar trials from prior to this time will be included as a reflection of evolving attitudes towards prospective trial registration.

Types of participants

We will include all adults (18 years and above) with functional or absolute non-anaemic iron deficiency. Non-anaemia is defined as haemoglobin (Hb) greater than 130g/l^{-1} for males and greater than 120g/l^{-1} for non-pregnant females. Studies that do not differentiate a Hb between males and females, and set a non-anaemic definition of greater than 120g/l^{-1} for both sexes will also be included.

In order to capture the broadest possible population, we have reviewed a series of RCTs from the existing literature to define iron deficiency, and have chosen the least restrictive definition (Beck-da-Silva 2013). Absolute or functional iron deficiency is defined as:

1. absolute iron deficiency: ferritin less than 30mg/l^{-1};
2. inadequate iron stores: ferritin less than 100mg/l^{-1};
3. functional iron deficiency: ferritin more than 100mg/l^{-1} and transferrin saturation (TSAT) less than 20%.

We will exclude pregnant and puerperal women because of considerable differences in the definition of anaemia in pregnancy.

Participants who have been treated with erythropoietin or other erythropoiesis-stimulating agents (ESA) alone or in combination with iron will be excluded.

Types of interventions

We will consider any study comparing any formulation of intravenous iron with placebo, or any two formulations of intravenous iron. We will consider all doses and preparations of intravenous iron. Oral iron preparations will be excluded from the review. This is because the therapeutic benefit of oral iron is difficult to assess due to the presence of multiple confounding factors (principally poor compliance due to side-effects, or malabsorption due to concomitant inflammation or duodenal pathology). This would introduce substantial and unquantifiable heterogeneity into the analysis, especially as the included trials will cover a wide range of patient populations, some of which, by definition, will be unable to take oral iron. In order to adequately assess the biological effect of iron loading across multiple patient groups, oral iron interventions are necessarily excluded.

We are aware that the wide range of intravenous iron preparations currently available implies that a network meta-analysis could be considered a superior methodology. However, the body of literature is unlikely to be large enough to justify this approach, although a future update of this review may uncover sufficient evidence to enable such an analysis. We will include a narrative table outlining the existing evidence, and the iron preparations used, in the full review.

Types of outcome measures

If trials have varied follow-up times we will consider separate analyses for primary and secondary outcome measures based on clinically meaningful time periods (short-, medium-, and long-term follow up).

Primary outcomes

1. Overall quality-of-life, taken at the end of follow-up, as measured by a quantitative quality-of-life measurement scale.
2. Haemoglobin concentration (g/l^{-1}), measured at the end of follow-up.

The outcomes chosen reflect key quantitative and qualitative endpoints for this intervention. Quality-of-life scoring systems have the ability to assess the clinical effects of iron replenishment separate from changes in haemoglobin concentration. There is considerable controversy in this area, particularly with respect to existing definitions of anaemia and evidence of continued haemoglobin response to iron replenishment despite haemoglobin concentration being apparently "normal" (Butcher 2017; Favrat 2014). Assessment of both a laboratory parameter of response to iron supplementation (haemoglobin concentration) and quality-of-life metrics will determine if observed improvements with iron supplementation in previous trials are related to improvements in haemoglobin concentration or another, as yet undefined, metric.

Secondary outcomes

1. Serum ferritin measured at the end of follow-up.
2. Peak oxygen consumption (VO_2 peak or VO_2 max), as measured by cardiopulmonary exercise testing taken at the end of follow-up.
3. Risk of bacterial infections. We will include this outcome from trials where there is a clear definition of how a bacterial infection was detected and where measurement occurred equally in both groups.
4. Risk of serious adverse events at the end of follow-up, defined as any event that would increase mortality; are life-threatening; require inpatient hospitalisation or result in persistent or significant disability; or any important medical events that might have jeopardised the participant or that require intervention to prevent them within 30 days of cessation of treatment (ICH-GCP 1996).
5. Risk of mild adverse events at the end of follow-up, defined as any event that does not meet the definition of a serious adverse event but that would require treatment or result in patient discomfort. Examples include headache, rash or nausea. Hypophosphataemia of any severity will be included in this category.

Information size calculation

For all meta-analyses performed, we will use trial sequential analysis software (Copenhagen Trial Unit 2016), in order to consider the adequacy of the power (Imberger 2015; Mascha 2015). We will use a type 1 error risk of 5% and a type 2 error risk of 10%, the pooled standard deviation for continuous data and unweighted mean of the control event rate for categorical data, and the diversity calculated from the actual meta-analysis.

Information size in meta-analysis can be considered similar to an a priori power calculation for a planned RCT, powered to observe a particular magnitude of effect. Hypothetical calculations for information size were undertaken using G*Power v3.1 for each of the primary outcome measures. It should be noted that these calculations do not take into account inherent heterogeneity between trials.

- Overall quality-of-life, taken at the end of follow-up: Favrat 2014 described mental quality-of-life scores (SF-12) taken at 56 days for intervention (47.3 ± 8.7) and control (45.1 ± 9.1). Based on this, an appropriately powered RCT to examine this effect size, with a type 1 error risk of 5% and a type 2 error risk of 10%, is 692.
- Concentration of haemoglobin, taken at the end of follow-up: Anker 2009 described haemoglobin concentration at 24 weeks for intervention (133 ± 1.0 $g.l^{-1}$) and control (132 ± 1.0 $g.l^{-1}$) groups. Based on this, an appropriately powered RCT to examine this effect size, with a type 1 error risk of 5% and a type 2 error risk of 10%, is 46.

Search methods for identification of studies

In order to reduce publication and retrieval bias we will not restrict our search by language, date or publication status.

Electronic searches

The Cochrane Injuries Group's Information Specialist will search the following databases:

1. Cochrane Central Register of Controlled Trials (which contains the Cochrane Injuries Trials Register) in the Cochrane Library (latest issue) (Appendix 1);
2. MEDLINE Ovid (1946 to present) (Appendix 2);
3. Embase Ovid (1947 to present) (Appendix 3);
4. Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to present) (Appendix 4);
5. Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to present) (Appendix 4);
6. Clinicaltrials.gov (www.clinicaltrials.gov) (Appendix 5);
7. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)(www.who.int/ictrp) (Appendix 6).

Searching other resources

We will screen the reference lists of all included studies and previous review articles for potential additional studies. We will also search Google Scholar and screen the first 300 results.

Data collection and analysis

We will conduct this review with adherence to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors (LFM and EL) will identify trials for inclusion independently of each other. We will resolve any disagreement between authors through discussion, or, if required, through involvement of a third author (DS). We will list excluded studies along with the reason for exclusion. We will investigate all eligible articles as full text. Where information in studies is unclear or missing we will contact the authors of individual trials directly for clarification and information.

Data extraction and management

Independent of one another, two review authors (LFM and EL) will extract data into a specifically-designed and pilot-tested form for this review, which will include the following.

1. Country of study participant recruitment
2. Year and language of publication
3. Year the trial was conducted
4. Study design
5. Sample size
6. Inclusion and exclusion criteria
7. Study population characteristics and clinical settings
8. Iron supplementation details, including dose, route, frequency and duration
9. Trial-specific outcomes
10. Outcomes included in this review
11. Information to assess the risk of bias
12. Details of prospective trial registration
13. Details of ethical review committee approval
14. Sources of support and trial funding

We will resolve discrepancies through discussion or by consulting a third author (DS) for a final decision.

Assessment of risk of bias in included studies

We will assess included studies for risk of bias according to the criteria outlined in Table 8.5.d in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The domains used to assess the risk of bias are: selection bias (random sequence generation and allocation concealment); blinding bias (blinding of participants and personnel and blinding of outcome assessment); attrition bias (amount, nature and handling of incomplete outcome data); reporting bias (selective reporting of outcome data); other bias (bias not covered elsewhere such as source of funding bias).

We will categorise individual studies as being at low, high or unclear risk of bias overall according to the following criteria:

1. low risk of bias (plausible bias unlikely to seriously alter the results);
2. unclear risk of bias (plausible bias that raises some doubt about the results); or
3. high risk of bias (plausible bias that seriously weakens confidence in the results).

Measures of treatment effect

We will use different treatment effects depending on the type of data. We will calculate the mean difference, with 95% confidence intervals (CIs), for continuous outcomes (e.g. iron store indices), and standardised mean difference (with 95% CIs) for assessing treatment effect in quality of life (taking into account different scales used across studies). We will use the risk ratio (RR) (with 95% CIs) to measure treatment effects for dichotomous variables. In the event that the events are rare, we will use Peto's odds ratio.

Unit of analysis issues

The unit of analysis will be the individual participant with iron deficiency who is undergoing treatment. As cluster trials or cross-over trials will not be considered, we do not anticipate any unit of analysis issues.

Dealing with missing data

We will contact all authors of the included studies with the aim to obtain missing information. Where no response is forthcoming, we will take the percentage of missing data into account when analysing and interpreting the results. If appropriate, we will estimate any such data from available information using the mean value from the relevant group for the required outcome. For continuous measures, where possible we will obtain SDs from other measures, such as standard errors (SEs), CIs, and P values.
For dichotomous measures, we will obtain proportions or percentages to estimate the number of events or participants assessed for that outcome.

Assessment of heterogeneity

Given a lack of common protocols used in research studies we expect a certain amount of clinical heterogeneity in included studies. This may be related to a number of factors but some potential sources of heterogeneity include variations in patient groups, different iron treatment regimens used and disparity in the quality of the study conduct. We will only compare clinically homogenous studies in the analysis. We will use the Chi^2 test to explore heterogeneity of included studies with a significant alpha level of 0.10. The heterogeneity will also be measured using the I^2 to quantify inconsistencies and D^2 to adjust information size calculations as part of trial sequential analysis (Wetterslev 2009).
In addition to statistical assessments, we will provide a descriptive assessment of heterogeneity as per the 'PICO' model as part of the discussion. We expect heterogeneity in a number of areas, necessitating the use of a random-effects model. Specific areas where heterogeneity is expected include the following.

- Population: marked differences in population are expected, ranging from otherwise healthy patients (Favrat 2014) to heart failure (Anker 2009).
- Intervention: different preparations and dosages of iron are expected. Whilst most modern treatment regimens contain fairly standardised dosages of elemental iron, it is not known what the effects of more historical preparations or regimens will be.
- Comparison: comparison will be limited to placebo. Minimal heterogeneity is expected.
- Outcomes: differences in quality-of-life scores used will manifest as some heterogeneity. It is hoped that the use of standardised mean difference will ameliorate some of this.

Assessment of reporting biases

We will perform an assessment of reporting and publication bias (between-studies) using visual inspection of funnel plots for asymmetry, followed up with Harbord or Egger's test (Harbord 2006; Egger 1997) if 10 or more studies are included in an analysis.

Data synthesis

If there are two or more trials with data for our defined outcomes, and data are sufficiently homogeneous, we will perform a meta-analysis. We will use the software package Review Manager 5.3 (RevMan 2014). We will calculate the effect estimate using a random-effects model. We will assess dichotomous variables using the Mantel-Haenszel test, or Peto's odds ratio if there are rare outcomes. We will assess continuous variables using the inverse variance method. We will report all results with a 95% confidence interval.
We will consider the estimate of heterogeneity in our interpretation of the results, including an assessment of how the quantity of heterogeneity, and its source, may have affected the reliability of our conclusions.
With respect to the secondary outcome measure of scoring systems for physical performance and mental well-being, we will transform standardised mean difference for quality-of-life measures back into a single outcome measure used by the highest number of patients included in the meta-analysis.
Where different scales are used for the assessment of continuous outcomes (i.e. quality-of-life scores), we will use the standardised mean difference.

Subgroup analysis and investigation of heterogeneity

We will perform the following two a priori subgroup analyses if there are more than two studies included in each analysis. The subgroup analyses will be performed for four categories of patients: those with heart failure, end-stage renal failure, preoperative populations, and 'other'. The 'other' category will include athletes, blood donors, people with inflammatory bowel disease and all other populations not included in the other three categories.

- Type of iron deficiency: we will perform this subgroup analysis with a focus on the form of iron deficiency that a participant is suffering from. This will include functional iron deficiency (any patient with a ferritin level of more than 100 to 300 μg/L and TSAT less than 20%) or absolute iron deficiency or inadequate iron stores (ferritin levels if less than 100 μg/L).
- Sex: we will perform this subgroup analysis to determine if there are any differences in the effect of intravenous iron based on sex.

Sensitivity analysis

We will conduct a sensitivity analysis on the primary outcome for each of the main analyses, by excluding any studies that demonstrated high or unclear risk of bias in any of the five domains. In the event that no study satisfied these criteria, we will consider unclear risk of bias in the selection, attrition, and reporting domains to be sufficient to include a study in a subsequent sensitivity analysis. Unclear or high risk of bias in the performance and detection bias domains will not be sufficient to exclude a study from subsequent

sensitivity analysis. This is because the characteristic colour of iron infusion is difficult to conceal, and hence inadvertent unblinding of participants and personnel to the intervention is possible unless adequate concealment measures are undertaken.

We will also assess the impact of any study that has a large effect size on the results of the meta-analysis, and assess the effects of missing data (Dealing with missing data).

Trial sequential analysis

We will perform trial sequential analysis to preserve the risk of type 1 and type 2 errors at desired levels in the setting of sparse data and potential repeated testing (Wetterslev 2009). For all meta-analyses performed, we will use trial sequential analysis (Copenhagen Trial Unit 2016), in order to consider the adequacy of the power and to adjust the 95% confidence intervals if the data are sparse (Imberger 2015; Mascha 2015). Preserving a type 1 error risk of 5% and a type 2 error risk of 10%, we will construct monitoring boundaries using the pooled standard deviation for continuous data and the unweighted mean of the control event rate for categorical data, and the diversity calculated from the actual meta-analysis.

Summary of findings

We will present the results of this review for all comparisons in a 'Summary of findings' table. We will include the following outcomes:

1. Mean difference (or standardised mean difference if different scales are used) in health-related quality of life.
2. Mean difference in concentration of haemoglobin (g/l^{-1}), taken at the end of follow-up.
3. Mean difference in ferritin, taken at the end of follow-up.
4. Mean difference in incidence of bacterial infection.
5. Mean difference in peak oxygen consumption (VO_2 peak or VO_2 max), taken at the end of follow-up.
6. Risk of serious adverse events (anaphylaxis, circulatory collapse, hospitalisation).
7. Risk of mild adverse events (headache, dizziness, rash, hypophosphataemia).

We will prepare the 'Summary of findings' table using GRADEpro GDT software (GRADEpro 2015). In accordance with the GRADE approach we will undertake an assessment of the quality of evidence for each outcome. We will examine the risk of bias within studies, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias, and assess the quality of evidence as either high, moderate, low or very low (Schünemann 2011).

In particular, we will consider the appropriateness of extrapolating our results from all patients with iron deficiency to the perioperative setting and how the indirectness in this interpretation is likely to decrease the certainty in any results.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Iron] this term only
#2 MeSH descriptor: [Iron Compounds] this term only
#3 MeSH descriptor: [Ferric Compounds] this term only
#4 MeSH descriptor: [Ferrous Compounds] this term only
#5 (iron or ferric* or ferrous)
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Injections, Intravenous] this term only
#8 (intravenous* or IV or inject*)
#9 #7 or #8
#10 #6 and #9
#11 (nonanemi* or nonanaemi* "non anemi*" or "non anaemi*" or NAID or IDNA)
#12 ("no anemia" or "no anaemia" or "not anemic" or "not anaemic" or "without anemia" or "without anemic" or "without anaemia" or "without anaemic")
#13 MeSH descriptor: [Iron] this term only and with qualifier(s): [Deficiency - DF]
#14 (iron depletion or iron deficien*)
#15 MeSH descriptor: [Anemia, Iron-Deficiency] this term only and with qualifier(s): [Prevention & control - PC]
#16 #11 or #12 or #13 or #14 or #15
#17#10 and #16
#18 MeSH descriptor: [Infant] explode all trees
#19 MeSH descriptor: [Child] explode all trees
#20 neonat* or newborn* or infant* or child* or schoolchild*
#21 MeSH descriptor: [Pregnancy] explode all trees
#22 pregnan* or postpartum
#23 #18 or #19 or #20 or #21 or #22
#24 #17 not #23

Appendix 2. MEDLINE Ovid search strategy

1. Iron/
2. Iron compounds/ or Ferric Compounds/ or Ferrous Compounds/
3. (iron or ferric* or ferrous).ti,ab,kw,rn.
4. or/1-3
5. Injections, Intravenous/
6. (intravenous* or IV or inject*).tw.
7. or/5-6
8. 4 and 7
9. (nonan?emi* or non an?emi* or NAID or IDNA).ab,ti.
10. ("no anemia" or "no anaemia" or "not anemic" or "not anaemic" or "without anemia" or "without anemic" or "without anaemia" or "without anaemic").ti,ab.
11. Iron/df
12. (iron depletion or iron deficien*).ti,ab,kf.
13. Anemia, Iron-Deficiency/pc
14. or/9-13
15. 8 and 14
16. randomi?ed.ab,ti.
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. placebo.ab.
20. clinical trials as topic.sh.
21. randomly.ab.
22. trial.ti.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. (animals not (humans and animals)).sh.
25. 23 not 24
26. 15 and 25
27. exp infant/
28. exp child/
29. (neonat*or newborn* or infant* or child* or schoolchild*).tw.
30. exp pregnancy/
31. (pregnan* or postpartum).ti.
32. or/28-31
33. 26 not 32

Appendix 3. Embase Ovid search strategy

1. iron therapy/
2. iron derivative/
3. ferric ion/
4. ferrous ion/
5. (iron or ferric* or ferrous).ti,ab.
6. or/1-5
7. exp intravenous drug administration/
8. (intravenous* or IV or inject*).tw.
9. or/7-8
10. 6 and 9
11. iron deficiency anemia/
12. iron deficiency/pc [Prevention]
13. (nonan?emi* or non an?emi* or NAID or IDNA).ab,ti.

14. ("no anemia" or "no anaemia" or "not anemic" or "not anaemic" or "without anemia" or "without anemic" or "without anaemia" or "without anaemic").ti,ab.
15. (iron depletion or iron deficien*).ti,ab.
16. or/11-15
17. 10 and 16
18. exp Randomized Controlled Trial/
19. exp controlled clinical trial/
20. exp controlled study/
21. comparative study/
22. randomi?ed.ab,ti.
23. placebo.ab.
24. *Clinical Trial/
25. exp major clinical study/
26. randomly.ab.
27. (trial or study).ti.
28. 18 or 19 or 20 or 22 or 23 or 24 or 25 or 26 or 27
29. exp animal/ not (exp human/ and exp animal/)
30. 28 not 29
31. 17 and 30
32. exp infant/
33. exp child/
34. (neonat*or newborn* or infant* or child* or schoolchild*).tw.
35. exp pregnancy/
36. exp postpartum hemorrhage/
37. (pregnan* or postpartum).ti.
38. or/32-37
39. 31 not 38

Appendix 4. Web of Science search strategy

#16 #14 Not #15
#15 TI= (mouse OR mice OR rat OR rats)
#14 #12 NOT #13
#13 TS=(pregnan* OR postpartum OR neonat* OR newborn* OR infant* OR child* OR schoolchild*)
#12 #11 AND #10
#11 TS=HUMAN
#10 #9 AND #8
#9 TS=((clinical OR control* OR placebo OR random OR randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random) SAME (trial* or group* or study or studies or placebo or controlled))
#8 #5 AND #6 AND #7
#7 TS= (intravenous* OR IV OR inject*)
#6 TS=(ferrous OR ferric OR iron)
#5 #1 OR #2 OR #3 OR #4
#4 TS= ("no anemia" OR "no anaemia" OR "not anemic" OR "not anaemic" OR "without anemia" OR "without anemic" OR "without anaemia" OR "without anaemic")
#3 TS=(non-anemic OR non-anaemic)
#2 TS="iron depletion"
#1 TS=("iron deficiencies" OR "iron deficiency" OR "iron deficient")

Appendix 5. ClinicalTrials.gov search strategy

Condition or disease = (non anaemic OR non anemic OR non anaemia OR non anemia OR no anemia OR no anaemia OR not anemic OR not anaemic OR without anemia OR without anemic OR without anaemia OR without anaemic) AND Other terms = iron AND (intravenous OR intravenous OR IV OR injection)

Appendix 6. WHO ICTRP search strategy

(non anaemic OR non anemic OR non anaemia OR non anemia OR no anemia OR no anaemia OR not anemic OR not anaemic OR without anemia OR without anemic OR without anaemia OR without anaemic) = condition AND iron = intervention

CONTRIBUTIONS OF AUTHORS

LFM drafted the initial protocol.

EL assisted in the revision of the protocol.

GI assisted in the revision of the protocol.

DS assisted in the revision of the protocol.

DECLARATIONS OF INTEREST

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EL: study drug for previous study provided by Vifor Pharma (Litton 2016). No other conflicts of interest.

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