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RESEARCH

Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials

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Abstract

Objectives To evaluate the efficacy and safety of intravenous iron, focusing primarily on its effects on haemoglobin, requirement for transfusion, and risk of infection.

Design Systematic review and meta-analysis of randomised controlled trials investigating the safety and efficacy of intravenous iron therapy.

Data sources Randomised controlled trials from Medline, Embase, and the Cochrane Central Register of Controlled Trials from 1966 to June 2013, with no language restrictions.

Eligibility criteria for selecting studies Eligible trials were randomised controlled trials of intravenous iron compared with either no iron or oral iron. Crossover and observational studies were excluded.

Main outcome measures Change in haemoglobin concentration and risk of allogeneic red blood cell transfusion (efficacy) and risk of infection (safety).

Results Of the 75 trials meeting the inclusion criteria, 72 studies including 10 605 patients provided quantitative outcome data for meta-analysis. Intravenous iron was associated with an increase in haemoglobin concentration (standardised mean difference 6.5 g/L, 95% confidence interval 5.1 g/L to 7.9 g/L) and a reduced risk of requirement for red blood cell transfusion (risk ratio 0.74, 95% confidence interval 0.62 to 0.88), especially when intravenous iron was used with erythroid stimulating agents (ESAs) or in patients with a lower baseline plasma ferritin concentration. There were no significant interactions between the efficacy of intravenous iron and type or dose administered. Intravenous iron was, however, associated with a significant increase in risk of infection (relative risk 1.33, 95% confidence interval 1.10 to 1.64) compared with oral or no iron supplementation. The results remained similar when only high quality trials were analysed.

Conclusions Intravenous iron therapy is effective in increasing haemoglobin concentration and reducing the risk of allogeneic red blood cell transfusion and could have broad applicability to a range of acute care settings. This potential benefit is counterbalanced by a potential increased risk of infection.

Introduction

Iron is essential for the production of red blood cells and is the most common nutritional deficiency worldwide, both in developed and developing countries.[1] Though allogeneic red blood cell transfusion might be lifesaving for the management of acute severe blood loss, there are increasing concerns about associated serious adverse events, costs, and scarcity.[2] Safe and effective strategies to reduce such transfusions are urgently needed.

Correction of iron deficiency anaemia with oral iron is limited by gastrointestinal absorption and is particularly ineffective in the setting of coexisting acute or chronic medical conditions.[3] Supported by laboratory results, intravenous iron therapy has an established role in the treatment of iron deficiency anaemia, when oral preparations are ineffective or cannot be used.[4] Recent advances in the understanding of iron metabolism and the association between allogeneic red blood cell transfusion and adverse outcomes has increased the interest in the use of intravenous iron to reduce requirement for red blood cell transfusion in various acute clinical settings.[5 6] Although older

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Appendix 1: Description of included studies
Appendix 2: Risk of bias in included studies
Appendix 3: Summary of main results

intravenous iron preparations were associated with a risk of anaphylaxis, newer preparations have largely alleviated this problem.[7] Nevertheless, whether intravenous iron is associated with other important adverse events, in particular the theoretical risk of infection, remains uncertain.[8-10]

In this systematic review and meta-analysis, undertaken according to PRISMA guidelines,[11] we evaluated the safety and efficacy of intravenous iron, focusing primarily on its effects on requirement for transfusion and risk of infection.

Methods

Eligibility criteria

We searched for randomised controlled trials in which intravenous iron was compared with either oral iron or no iron supplementation. Studies were excluded if they were randomised but with a crossover design, observational, did not report an outcome of interest, provided insufficient data for outcomes to be reported, or did not contain a group or subgroup in which the independent effect of intravenous iron could be assessed. The primary outcomes of interest were change in haemoglobin concentration and risk of transfusion (efficacy) and risk of infection (safety). Secondary outcomes of interest included adverse events and serious adverse events as defined by the primary studies, anaphylaxis, mortality, length of hospital stay, cost, and cost effectiveness.

Search strategy

The primary search was conducted with Medline, Embase and the Cochrane Central Register of Controlled Trials for randomised trials with the terms "iron" and "ferric compounds" and "intravenous." The search included the time period from 1966 to June 2013 and was conducted without language restrictions. We searched the reference lists of all included studies as well as relevant review articles and conference proceedings. The manufacturers of intravenous iron formulations were also contacted to request access to unpublished trial data.

Two authors (EL and JX) independently conducted the primary search. When we were uncertain about eligibility or needed additional data on endpoints, we contacted the corresponding author to request further information.

Study selection

Two authors (EL and JX) retrieved potentially relevant titles for full text review and transcribed data from eligible studies onto a prespecified proforma. Studies that were published only in abstract form were excluded. Disagreement on study inclusion or endpoints was resolved by the third author (KMH).

Data analysis

Our primary outcomes of interest were efficacy (change in haemoglobin concentration and proportion of patients requiring allogeneic red blood cell transfusion) and safety (all cause infection). When studies included both oral iron and no iron comparison groups, we preferentially compared intravenous iron with oral iron. For categorical data, the risk of an outcome was defined as the number of patients with an event compared with the number of patients with and without an event. For continuous data, we used mean, standard deviation, and participant number. Data from studies fulfilling the eligibility were pooled for meta-analysis with a random effects model. Studies with no events in one of the study groups were included as this has been shown to provide a more valid estimate of true treatment effect.[12] We calculated standardised mean difference and risk ratio with 95% confidence interval for continuous and categorical outcomes, respectively, and $P<0.05$ was taken as significant. Heterogeneity was assessed with the I^2 statistic, and $I^2>40\%$ was considered as significant heterogeneity. Meta-regression was undertaken to examine the effect of intravenous iron dose and baseline iron on the associations between intravenous iron and the primary outcomes.

We carried out a sensitivity analysis on the efficacy (transfusion) and safety (infection) outcomes by excluding studies with a high risk of bias for one or more key domains using the Cochrane Collaboration's tool for assessing risk of bias.[13] Publication bias was assessed with a funnel plot, plotting the odds ratio for proportion transfused against the standard error of the log odds ratio. The statistical analysis was conducted with Stata (Intercooled Version 11.2, StataCorp, College Station, TX, USA) and Comprehensive Meta-analysis (version 2.2.034, Biostat, USA, 2006).

Results

The initial electronic search returned 1815 citations. After examination of the titles and abstracts, we retrieved 126 for more detailed examination. A total of 75 studies including 10 879 participants fulfilled the inclusion criteria and were included in the systematic review (appendix 1).[14-88] Of the included studies, 72 including 10 605 participants provided sufficient quantitative outcome data to be included in the primary meta-analyses. Figure 1 show details of study inclusion⇓.

Study characteristics and validity assessment

The number of participants in the included studies varied between 25 and 507, and studies were carried out in a wide range of clinical specialties (renal n=19, obstetric n=19, surgical n=11, oncology/haematology n=11, cardiology n=4, gastroenterology n=4, other n=7). The baseline haemoglobin concentration (mean range 60-145 g/L) and ferritin concentration (mean range ferritin 70-7610 ng/mL), of the included patients also varied between studies. The most common intravenous iron preparation used in the included studies was iron sucrose (n=42), followed by iron gluconate (n=10) and ferric carboxymaltose (n=10). Dextran iron was used in seven studies; six further studies used other iron preparations. Efficacy outcomes, including change in haemoglobin concentration and transfusion, were variably reported, as were safety outcomes including infection, mortality, serious adverse events, and anaphylaxis. Appendix 1 shows the characteristics of the included studies.

Overall, the risk of bias was low for 18 studies and high for 57 studies. The overall high risk of bias was accounted for by most studies not being blinded to participants or study personnel (n=56).

The authors of nine studies provided addition data for inclusion in the systematic review. Appendix 2 shows the results of the validity assessment.

Quantitative data synthesis

Change in haemoglobin concentration and proportion of patients requiring allogeneic red blood cell transfusion

A total of 59 studies comprising 7610 participants reported the change in haemoglobin concentration before and after treatment (appendix 3). When data were pooled, intravenous iron was associated with a significant increase in standardised mean haemoglobin concentration (6.5 g/L, 95% confidence interval

5.1 g/L to 7.9 g/L) compared with oral iron or no iron supplementation (fig 2⇓). There was significant heterogeneity between the studies (I^2=87.7%, P<0.01).

A total of 22 studies comprising 3321 participants reported on the risk of requiring allogeneic red blood cell transfusion. Intravenous iron therapy was associated with a significant reduction in risk (risk ratio 0.74, 95% confidence interval 0.62 to 0.88), without significant heterogeneity (I^2=9%, P=0.3; fig 3⇓).

There was a potential interaction between use of erythroid stimulating agents and the effect of intravenous iron therapy, with a greater effect of intravenous iron on reducing risk of requiring transfusion with concurrent use of erythroid stimulating agents (slope of the regression line 0.32, 95% confidence interval 0.02 to 0.63; P=0.04; fig 4⇓). Similarly, a lower baseline ferritin concentration was associated with greater therapeutic effect in reducing the risk ratio of requiring red blood cell transfusion after intravenous iron therapy (slope of the regression line 0.002, 95% confidence interval 0.002 to 0.004; P=0.04). There was, however, no interaction between baseline transferrin saturation and risk of requiring red blood cell transfusion after intravenous iron therapy.

Effect of intravenous iron on all cause infection

After we excluded three studies with no events in both intervention and comparison groups,[45-74] 24 studies (n=4400) reported data on risk of infection after intravenous iron compared with either oral iron or no iron supplementation (appendix 3). Intravenous iron was associated with a significant increase in risk of infection of 1.33 (95% confidence interval 1.10 to 1.64; figure 5⇓), with no significant heterogeneity (I^2=22.7%, P=0.2).

Increased risk of infection was observed in studies comparing intravenous iron with oral iron and in those comparing intravenous iron with no iron. There was no interaction between baseline ferritin, transferrin saturation, iron per dose, or erythroid stimulating agents and risk of infection.

Effect of intravenous iron therapy on other safety endpoints

There was no significant difference in mortality (risk ratio 1.1, 95% confidence interval 0.8 to 1.5) or serious adverse events (1.1, 0.9 to 1.2) with intravenous iron therapy in 20 and 19 trials, respectively. Adverse events were also not significantly different between intravenous iron therapy and oral iron or no supplemental iron (0.9, 0.8 to 1.1). Of the 32 studies that on reporting anaphylaxis, there were eight cases in participants receiving intravenous iron (n=2186).

Sensitivity analysis and publication bias

Exclusion of studies with high risk of bias according to the Cochrane Collaboration's tool for assessing risk of bias[13] limited the meta-analysis of risk of transfusion to only five studies (n=901),[34-78] and this did not change the direction of the association between intravenous iron and risk of requiring allogeneic red blood cell transfusion, but the association was no longer significant (risk ratio 0.8, 95% confidence interval 0.6 to 1.1; P=0.66). The sensitivity analysis for risk of infection limited the meta-analysis to eight studies[20-78] and did not substantially change the direction and magnitude of the association between intravenous iron therapy and risk of infection (1.4, 1.0 to 1.8; P=0.03). There was no evidence of publication bias in reporting requirement for allogeneic red blood cell transfusion in the pooled studies (fig 6⇓).

Discussion

In this large systematic review and meta-analysis assessing safety and efficacy in patients in many specialties we have shown that intravenous iron is effective in increasing haemoglobin concentration and reducing the risk of allogeneic red blood cell transfusion but is associated with an increased risk of all cause infection. Intravenous iron is increasingly advocated to treat anaemia with the aim of reducing the need for allogeneic red blood cell transfusion; the risks and benefits of intravenous iron, however, remain uncertain.

Reducing requirement for allogeneic red blood cell transfusion

Allogeneic red blood cell transfusion is associated with an increased risk of serious adverse events, including mortality.[89] In this meta-analysis, we confirmed that intravenous iron is effective in reducing the requirement for red blood cell transfusion and thereby reducing associated risk. This benefit seemed consistent across different categories of disease and formulations of intravenous iron and was present whether intravenous iron was compared with oral iron or no iron. These findings are in keeping with recent advances in the understanding of iron metabolism; intravenous iron is more effective than oral iron, particularly in the setting of acute or chronic inflammation, by bypassing the effects hepcidin—an inhibitor of gastrointestinal iron absorption.[90] As such, intravenous iron might have an important role in the management of patients as part of a strategy to reduce requirement for allogeneic red blood cell transfusion for many patients in hospital.

Additionally, we have shown that the effect of intravenous iron on the risk of requiring allogeneic red blood cell transfusion can be further enhanced by concomitant use of erythroid stimulating agents. None of the studies included in the transfusion meta-analysis were conducted in patients with chronic renal failure, in whom use of erythroid stimulating agents is standard. The use of these agents alone could induce a state of functional iron deficiency and has been postulated as a potential mechanism for the negative results of previous studies on use of erythroid stimulating agents in critical care.[91 92] Whether the addition of intravenous iron to erythroid stimulating agents in this setting is beneficial requires further investigation.

Iron and risk of infection

The reduction in allogeneic red blood cell transfusion must be considered alongside our finding of an increased risk of all cause infections after intravenous iron therapy. Free iron has been shown to potentiate bacterial growth in vitro.[8] Clinical evidence on the association between intravenous iron therapy and infection, however, has been inconclusive, with no increase in infection observed with intravenous iron therapy in patients undergoing dialysis or in patients after surgery or in a mouse model of critical care anaemia.[9-94] This discrepancy might be explained by the low free iron concentrations associated with newer intravenous iron preparations.[95 96] Our finding might also be a false positive result. Infection was not a predefined endpoint in many pooled studies, and it is possible that missing data could have created unmeasured bias in our analysis. Furthermore, we could not find a significant association between iron dose and risk of infection, and, overall, serious adverse events and mortality were not significantly increased in those receiving intravenous iron compared with oral or no iron. Until randomised controlled trials of intravenous iron adequately powered for patient centred outcomes are available, including

standardised definitions for infection, it might be preferable to use intravenous iron preparations associated with relatively low free iron concentrations.

Although this was a large comprehensive systematic review, several limitations bear consideration. Firstly, data on all outcomes were not available from each study, and the doses and preparations of intravenous iron used in the pooled studies varied. Nevertheless, heterogeneity in the risk of requiring transfusion and infection was low, and the number of studies available was sufficient to conduct several meta-regression analyses to assess the interaction between different predictors and efficacy of intravenous iron therapy in increasing haemoglobin concentration. Previous smaller systematic reviews of intravenous iron therapy were unable to provide sufficient data to estimate important outcomes such as risk of infection or to assess the effect of different predictors on efficacy.[97 98] Secondly, the quality of the included studies was variable, and the overall risk of bias in the included studies was high, despite exclusion of studies that had not been published in full. Finally, meta-regression of trial characteristics with participant level characteristics, such as baseline ferritin concentration, could lead to aggregation bias and might be underpowered to detect true differences, such as the effect of type and dose of intravenous iron.[99] We included a large number of studies and conducted meta-regression only when heterogeneity was low on forest plot based on an a priori defined criterion of non-significant heterogeneity (I^2<40%), which reduces but cannot completely exclude the risk of bias.

Conclusion

Intravenous iron therapy is associated with a significantly reduced risk of need for an allogeneic red blood cell transfusion. These findings suggest that intravenous iron might have broad applicability to many patients in hospital, in whom anaemia is common. This benefit is counterbalanced by a potential increased risk of infection. Further randomised controlled trials of intravenous iron are required to define whether it should be used as a first line treatment to reduce allogeneic red blood cell transfusions in patients in hospital. Such trials should include well defined infection endpoints and be adequately powered for important patient centred endpoints including mortality and major morbidity.

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Contributors: EL had the concept for the study, EL and KMH designed the study, EL JX, and KMH conducted the analysis, interpretation of the data and drafted the manuscript. EL, JX, and KMH all approved the final version to be published. EL is guarantor.

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What is already known on this topic

Intravenous iron therapy is effective at increasing haemoglobin concentration in patients with iron deficiency anaemia

What this study adds

Intravenous iron therapy can effectively reduce the need for red blood cell transfusion across a range of acute care settings

The benefit of intravenous iron in increasing haemoglobin concentration was seen when compared with both oral iron and no iron supplementation and was more effective when used with erythroid stimulating agents and in patients with lower baseline plasma ferritin concentrations

Intravenous iron therapy was associated with an increased risk of infection

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Figures

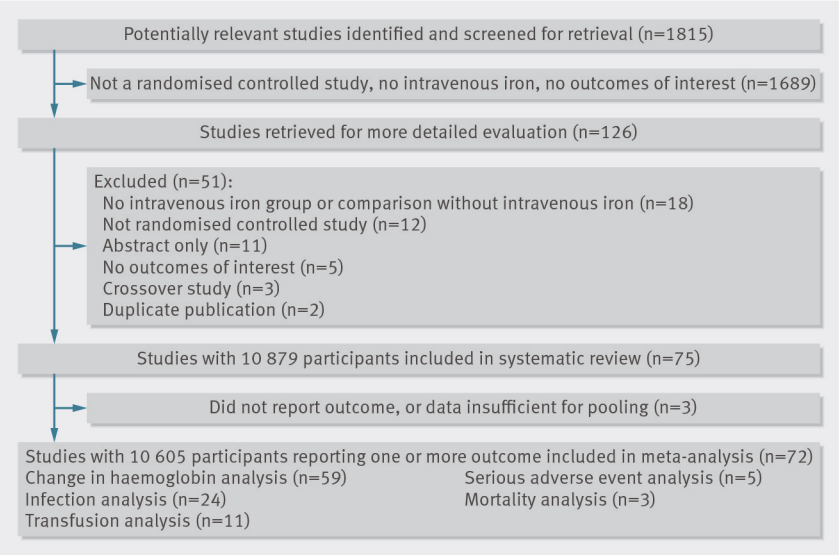

Fig 1 Flow diagram of selection of studies on intravenous iron therapy

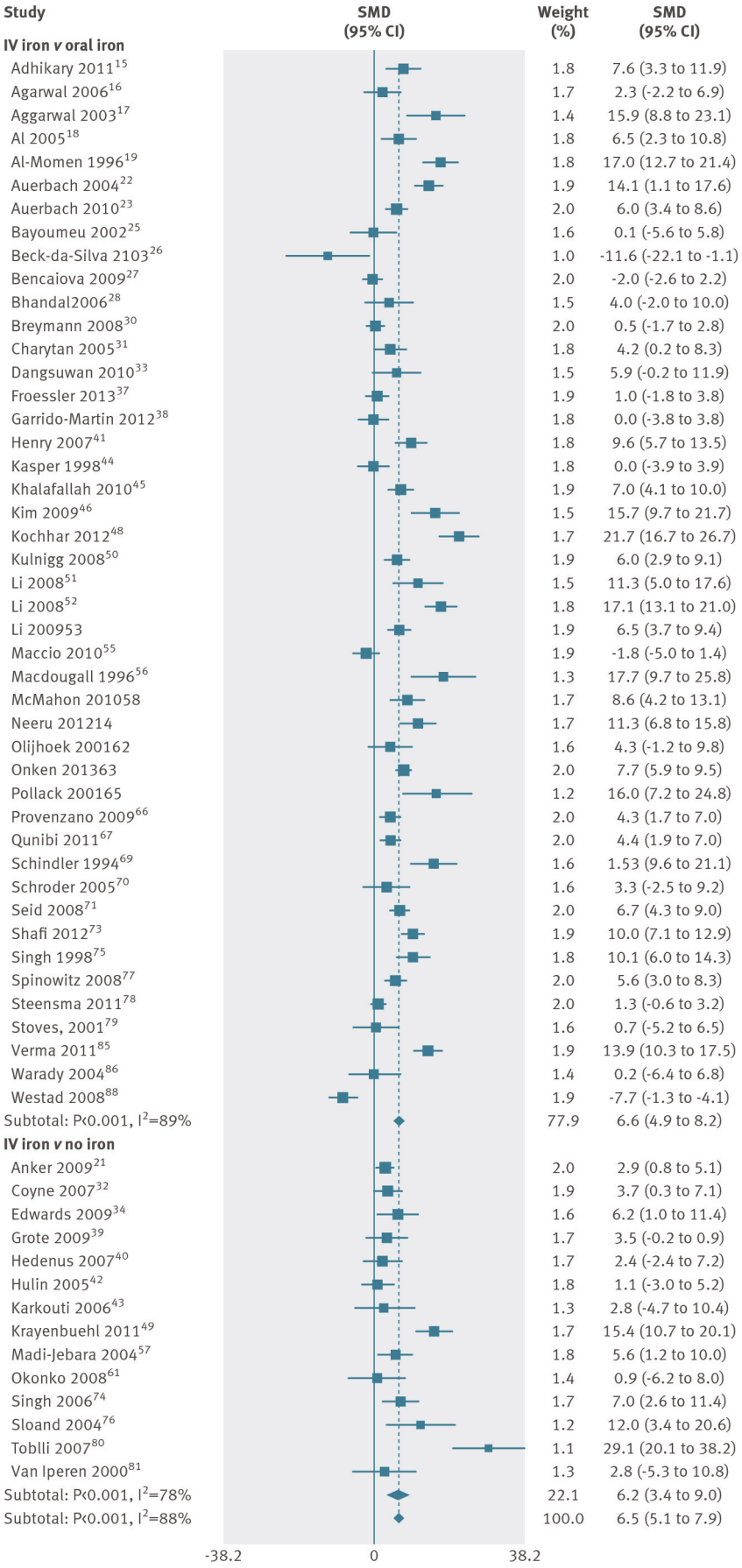

Fig 2 Standardised mean difference in haemoglobin (g/L) in patients who received intravenous iron compared with oral iron and no iron. Weights are from random effects analysis

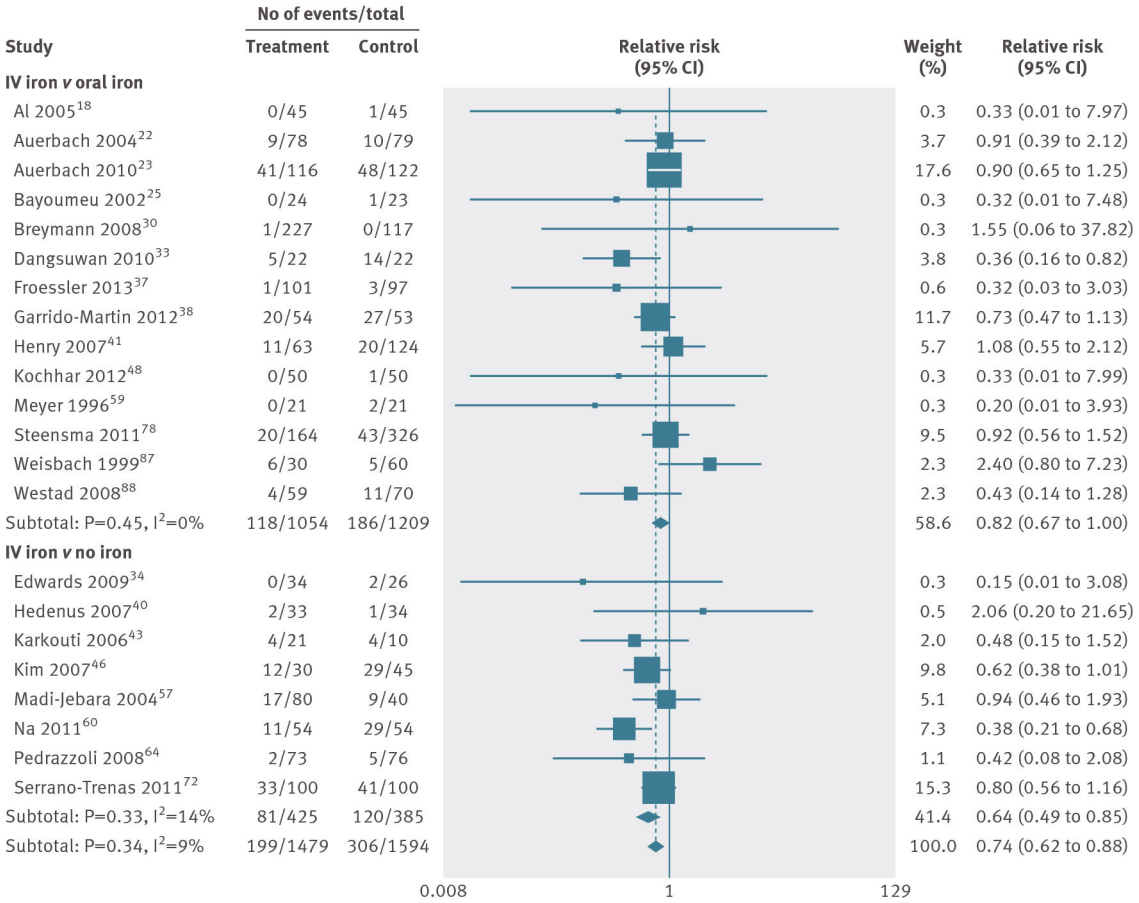

Fig 3 Risk of red blood cell transfusion in patients who received intravenous iron compared with oral iron and no iron. Weights are from random effects analysis

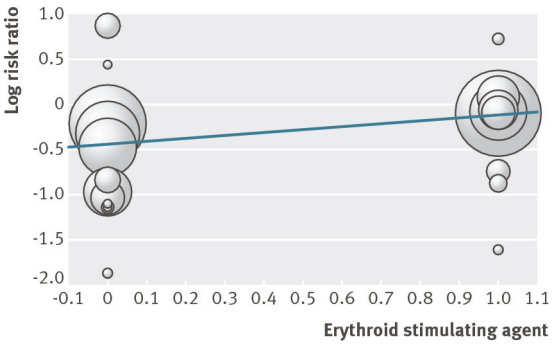

Fig 4 Regression of erythroid stimulating agent on log risk ratio of red blood cell transfusion. Slope of regression line 0.32, 95% confidence interval 0.02 to 0.63; P=0.04)

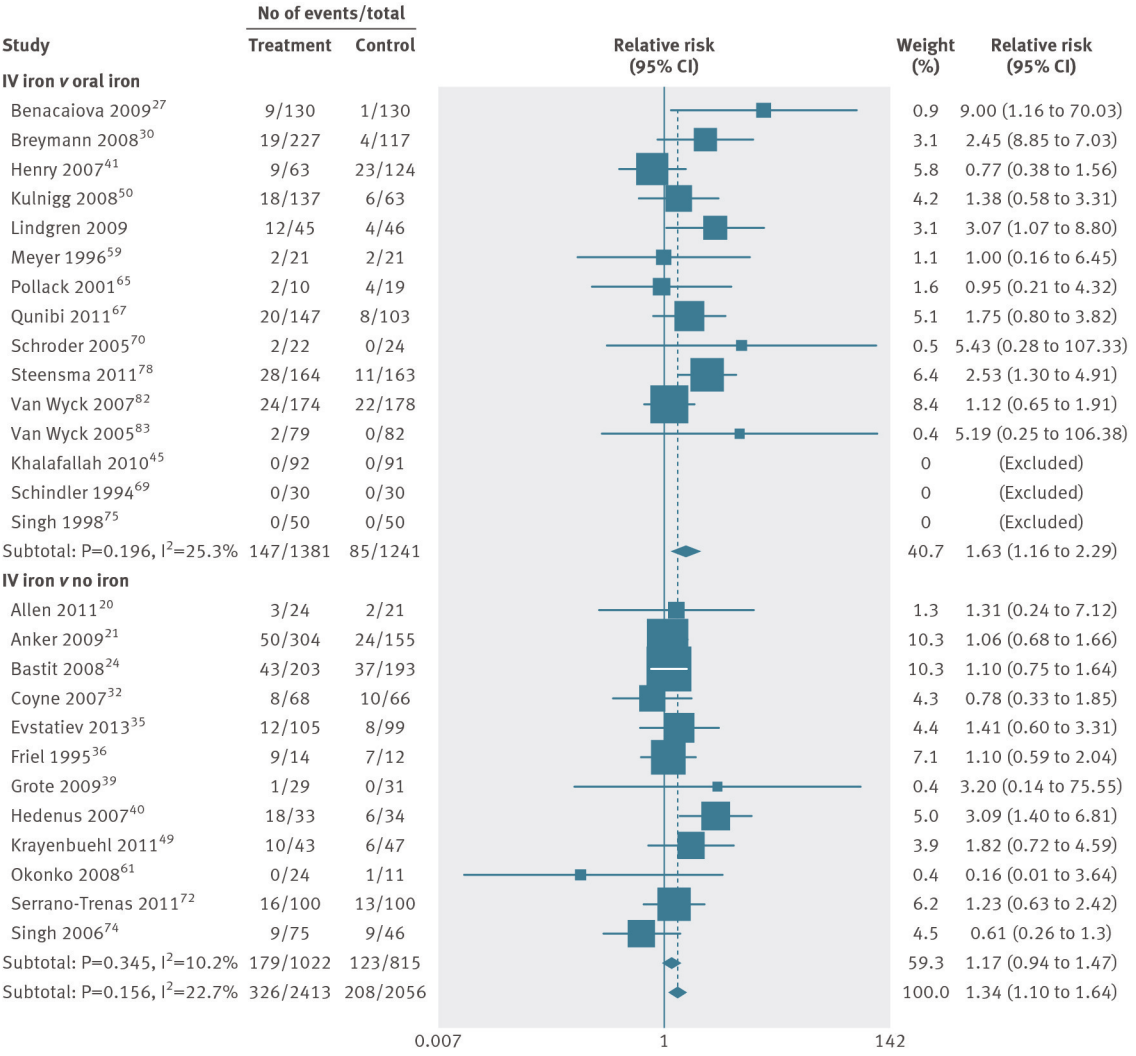

Fig 5 Risk of infection in patients who received intravenous iron. Weights are from random effects analysis

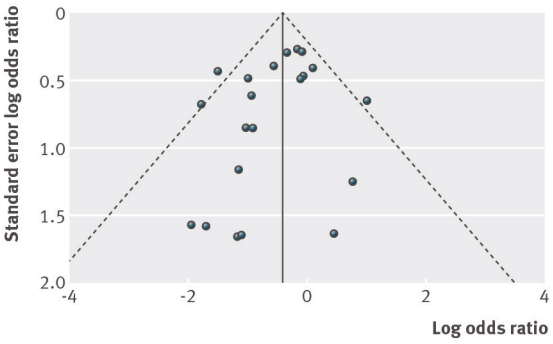

Fig 6 Odds ratio of transfusion against standard error of log odds ratio